Chapter IV

$N$-Substituted 4'-coumarinyl-1-isoquinolyl methanes – Synthesis and Biological evaluation
4.0. Introduction

The work to be described in this chapter is related to the functionalization of the secondary ring nitrogen of isoquinoline. Hence it is pertinent to survey the biological and structural importance of $N$-substituted isoquinolines containing different groups at C-1 position of isoquinoline.

In continuation of previous chapters it was planned to synthesize $N$-substituted tetrahydridoisoquinolines since wide range of $N$-substituted 1,2,3,4-tetrahydroisoquinolines has been found to be a useful starting materials for the construction of a variety of medicinally attractive intermediates. Many naturally occurring tetrahydroisoquinolines alkaloids have been found to possess antihypertensive, hemostatic, smooth or skeletal muscle relaxant, antispasmodic, antitussive, antimalarial, narcotic, analgesic or antipyretic activities. Few $N$-acyl derivatives of papaverine and related compounds show variety of activities against AIDS, glaucoma and fungal infections.

Importance of $N$-substituted isoquinolines

The above-said compounds can be represented by the general structure I.

In naturally occurring isoquinolines the group $R_2$ is generally benzyl with methoxy or hydroxyl function.

In the present context the group $R_1$ is restricted to an amide or a thioamide in view of their biological importance.

Recently Ramesh Chandra et al. have synthesized a series of $N$-carbamoyl/thiocarbamoyl isoquinolines 1 and 2 , and studied their antispasmodic activity and established structure activity relationship.
Kumar et al.,\textsuperscript{10} have reported some new substituted triazino tetrahydroisoquinolines 3 and 4 as novel antileishmanial agents, which do not possess any substituents at C-1.

Mokrosz et al.,\textsuperscript{11} have reported 1,2,3,4-tetrahydroisoquinolines 5 as a new class of 5-HT\textsubscript{1A} receptor ligands. It has been observed that the nitrogen atom in the tetrahydroisoquinoline would mimic the basic N-4 atom in 1-arylpiperazine (example buspirone 6) at 5-HT\textsubscript{1A} receptor binding site.\textsuperscript{12} Additionally it has been suggested that the basic nitrogen atom and the terminal cycloimide moiety were directly responsible for the formation of a bioactive complex as well as for the functional profile of the buspirone molecule at 5-HT\textsubscript{1A} receptors.
Yuen et al.,\textsuperscript{13} have established structure activity relationship of substituted 1,2,3,4-tetrahydroisoquinolines 7 as N-Type calcium channel blockers.

![Chemical structure of 7]

Gitto et al.,\textsuperscript{14} have reported some N-substituted tetrahydroisoquinolines 8 as anticonvulsant agents. Some structurally related promising Non-competitive AMPA receptor antagonists 9-12 are given.

- 8: GYKI 52466
- 9: Talampanel
- 10: Talampanel
- 11: 12a: X = O (CFM-2)
- 12b: X = S (CFM-2S)
Some 1-dialkylaminomethyl-2-substituted tetrahydroisoquinolines (13-14) represent novel class of potent antinociceptive agents with varying degrees of selectivity for κ and μ opioid receptors.\textsuperscript{15}

\[ \begin{align*}
13 & \quad Ar = \text{Substituted phenyl} \\
& \quad R_1, R_2 = \text{linear or cyclic alkyl}
\end{align*} \]

\[ \begin{align*}
14a & \quad X = \text{OMe, OH, (OH)}_2, \text{Me, SMe, Cl, F}, R = \text{H} \\
14b & \quad X = \text{H}, R = \text{Me, SMe}
\end{align*} \]

Synthesis of \( N \)-benzylisoquinoline alkaloid bernumicine 16 has been achieved via (±)-Salsoline 15 prepared by Pictet-Spengler condensation. Resolution of this with L- (+)-tartaric acid yielded (R)(+) salsoline 15, which reacted with 3,4-dimethoxy-benzyl toluene sulfonate to give (R)(+)-bernumicine 16, identical with the natural alkaloid. Similarly (R)(+)-bernumidine 17 has been prepared.\textsuperscript{16}

\[ \begin{align*}
15 & \quad \text{MeO} \\
& \quad \text{MeO, Me}
\end{align*} \]

\[ \begin{align*}
16 & \quad \text{MeO} \\
& \quad \text{MeO, Me}
\end{align*} \]

\[ \begin{align*}
17 & \quad \text{MeO} \\
& \quad \text{MeO, Me}
\end{align*} \]

The new 2-benzylisoquinoline alkaloid heterocarpine 18 has been isolated from \textit{Ceratocarpnos heterocarpa}\textsuperscript{17} and its structure has been confirmed by its synthesis from the iminium salt 19, through the tetrahydroisoquinoline 20a and 20b and 20c
Salcinol and the new alkaloid $N$-(6-fructopyranquinolines)-salcinol 21a and the unnamed 1,1-dimethyltetrahydroisoquinolines 21b and 22, the structures of which are deduced from their spectra, have been isolated from *Aristolochia arcuata*.18

$N$-substituted derivatives of nornarcotine, such as 23 have been prepared as potential adjuvant for vaccines17 and simpler carbamates, such as 24 have been shown to act as modulators of the GABA$_A$ receptor.18

The hitherto surveyed literature offers greater possibilities of introducing different groups at the isoquinoline nitrogen. The present work of $N$-functionalization of the coumarin analogues of the tetrahydroisoquinoline alkaloids will be described in the next section.
4.2. PRESENT WORK

The work carried out during the present investigation is described in the form of a following scheme 1. This describes the synthesis of aryl, naphthyl and ethyl substituted N-amides and thioamide derivatives of coumarin analogues of tetrahydroisoquinolines.

The required starting material 7 was synthesized according to the procedure described in chapter II. This 1,2,3,4-tetrahydroisoquinoline 7 was further exploited to synthesize various substituted N-amides and N-thioamides derivatives by treating it with various substituted isocyanates and isothiocyanates.

All these nucleophilic additions to isothiocyanates and isocyanates were found to occur at room temperature in acetonitrile.

Treatment of substituted isothiocyanates and isocyanates afforded the 1-(2-Oxo-2H-chromen-4-yl-methyl)-3,4-dihydro-1H-isoquinoline-2-carbothioic acid phenylamide and 1-(2-Oxo-2H-chromen-4-yl-methyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid phenylamide 10 respectively in good yield.

Ethyl isothiocyanates when reacted with 7 furnished 1-(2-Oxo-2H-chromene-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carbothioic acid ethylamide 11 in better yields.

Upon treating of the 1-Naphthyl isocyanate and isothiocyanate with 7 yielded the corresponding amides 1-(2-Oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid naphthalene-1-ylamide and 1-(2-Oxo-2H-chromen-4-yl-methyl)-3,4-dihydro-1H-isoquinoline-2-carbothioic acid naphthalene-1-ylamide 12 in moderate yield.

All the synthesized compounds were purified by the recrystallization from a suitable solvents and the purity was checked by TLC. All the title compounds have been studied for their spectral properties like IR, NMR and Mass spectra.
The preliminary anti-microbial evaluation has been carried out against three Gram-positive and three Gram-negative bacterial strains, and against two fungal strains.

4.3. RESULT AND DISCUSSION

The required 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one \(7b\) and 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one \(7a\) were synthesized according to the procedure given in chapter II.

The nucleophilicity of the nitrogen of the 1,2,3,4-tetrahydroisoquinoline \(7\) was exploited to synthesize various substituted \(N\)-amides and \(N\)-thioamides \(10, 11\) and \(12\) by treating \(7\) with various substituted isocyanates and isothiocyanates of phenyl, ethyl and naphthyl respectively.

The condensation of \(7\) with various substituted phenyl isocyanates and phenyl isothiocyanates in acetonitrile led to the formation of the product \(10\). In IR spectra a strong band around \(v_{\text{N-H}}\) 3300 – 3200 cm\(^{-1}\) due NH coupled with a band around \(v_{\text{C=O}}\) 1640 cm\(^{-1}\) due to amide carbonyl indicates the formation of the product \(10\) obtained by the treatment of phenyl isocyanates with \(7\) whereas the products obtained by phenyl isothiocyanates do show a strong band around \(v_{\text{N-H}}\) 3370 – 3300 cm\(^{-1}\) due to NH but they lack a band around \(v_{\text{C=O}}\) 1640 cm\(^{-1}\) due to carbonyl stretching rather a band around \(v_{\text{C=S}}\) 1190 – 1270 cm\(^{-1}\) is observed, however it is tedious to assign as it appears in finger print region that coupled with many other bands.

The compounds \(10, 11 \text{ and } 12\) are analogues of secondary amides and they show an amide band II in the region 1570 – 1515 cm\(^{-1}\) that is at lower frequencies than their primary counterparts. In these compounds often hydrogen bonding is operative as a result a free NH band is replaced by multiple bands in 3350 – 3150 cm\(^{-1}\).
Scheme 1

10a $R_1 = R_2 = R_3 = H, X = S$
10b $R_1 = R_2 = R_3 = H, X = O$
10c $R_1 = R_2 = OCH_3, R_3 = H, X = S$
10d $R_1 = R_2 = OCH_3, R_3 = H, X = O$
10e $R_1 = R_2 = H, R_3 = 4\text{-}Cl, X = S$
10f $R_1 = R_2 = H, R_3 = 4\text{-}Cl, X = O$
10g $R_1 = R_2 = OCH_3, R_3 = 4\text{-}Cl, X = S$
10h $R_1 = R_2 = OCH_3, R_3 = 4\text{-}Cl, X = O$
10i $R_1 = R_2 = H, R_3 = 2,4\text{-}\text{difluoro}, X = S$
10j $R_1 = R_2 = H, R_3 = 2,4\text{-}\text{difluoro}, X = O$
10k $R_1 = R_2 = OCH_3, R_3 = 2,4\text{-}\text{difluoro}, X = S$
10l $R_1 = R_2 = OCH_3, R_3 = 2,4\text{-}\text{difluoro}, X = O$
10m $R_1 = R_2 = H, R_3 = 4\text{-}Br, X = S$
10n $R_1 = R_2 = OCH_3, R_3 = 4\text{-}Br, X = S$
10o $R_1 = R_2 = H, R_3 = 2\text{-}Br, X = S$
10p $R_1 = R_2 = OCH_3, R_3 = 2\text{-}Br, X = S$
10q $R_1 = R_2 = H, R_3 = 2\text{-}Cl, X = S$
10r $R_1 = R_2 = OCH_3, R_3 = 2\text{-}Cl, X = S$
10s $R_1 = R_2 = H, X = S$
10t $R_1 = R_2 = OCH_3, X = S$
10u $R_1 = R_2 = H, X = O$
10v $R_1 = R_2 = OCH_3, X = O$
10w $R_1 = R_2 = H, X = S$
10x $R_1 = R_2 = OCH_3, X = S$
10y $R_1 = R_2 = H, X = O$
10z $R_1 = R_2 = OCH_3, X = O$
Since amide group can form dimers with a *cis* conformation the $\nu_{C=O}$ absorption of amides shows itself at lower frequencies than "normal" carbonyl absorption due to resonance effect and hydrogen bonding.

In $^1H$ NMR spectra, characteristically C1 proton appears downfield in the range $\delta$ 6.2 – 6.5 and owing to the diastereotopicity $\alpha$-CH$_2$ protons they appeared as complex multiplets in the region $\delta$ 3.75 – 4.0 ppm. C3 and C4 proton showed magnetic non-equivalence. Axial and equatorial protons appeared as separate signals with complex splitting pattern in the region $\delta$ 2.9 – 3.3. All other protons appeared in the expected regions.

In compound 11, the ethyl group showed characteristic triplet ($\delta$ 1.26) and quartet ($\delta$ 3.77) with all other diagnostic signals. In compound 12 also IR, $^1H$ and $^{13}C$ NMR confirm the formation of the product.

$^1H$ and $^{13}C$ NMR assignment for the representative compound is given in figure 1.

**Figure 1.**

*Assignment of $^1H$ NMR of 10a*

<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical Shift (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>2.41 (s, 3H)</td>
</tr>
<tr>
<td>H3a</td>
<td>2.96 - 3.0 (m, 1H)</td>
</tr>
<tr>
<td>H4e</td>
<td>3.0 - 3.11 (m, 1H)</td>
</tr>
<tr>
<td>H4a</td>
<td>3.31 (m, 1H)</td>
</tr>
<tr>
<td>H3a</td>
<td>3.80 (m, 1H)</td>
</tr>
<tr>
<td>H3e &amp; H4a</td>
<td>4.0 - 4.04 (m, 2H)</td>
</tr>
<tr>
<td>H3r</td>
<td>5.70 (s, 1H)</td>
</tr>
<tr>
<td>H1</td>
<td>6.48 (m, 1H)</td>
</tr>
<tr>
<td>Hh</td>
<td>8.31 (s, 1H)</td>
</tr>
<tr>
<td>H*</td>
<td>6.48 - 7.38 (m, 12H)</td>
</tr>
</tbody>
</table>

In compound 10a all the aromatic protons appeared as multiplet in the range of $\delta$ 6.48 – 7.38 whereas the C3'-H appeared at $\delta$ 5.70 upfield and C1-H$_1$
has appeared downfield compared to its precursor 7a. This assignment has been made on the basis of the 2D NMR.

The assignment of $^{13}$C NMR spectrum of compound 10a has been given in figure 2. C1, C2, C3, C4, Ca and CH$_3$ carbons have appeared in the range $\delta$ 60-20. All other aromatic protons have observed in the range $\delta$ 117 - 182. The $\delta$ 182 can be assigned to amide carbonyl carbon and $\delta$ 161 to lactone carbonyl carbon.

**Figure 2.**

**Assignment of $^{13}$C NMR of 10a**

The spectral and analytical data for all the remaining compounds are given in experimental section of this chapter.
Spectrum No. 1. IR (KBr) of compound 10a.

Spectrum No. 2. $^1$H NMR (CDCl$_3$) of compound 10a.
Spectrum No. 2. $^1$H NMR (CDCl$_3$) of compound 10a (Expansion)

Spectrum No. 3. $^{13}$C NMR (CDCl$_3$) of compound 10a.
Spectrum No. 4. 2D HETCOR of compound 10a.

Spectrum No. 5. LC MS chromatogram of compound 10a.
Spectrum No. 5. LC MS of compound 10a.

Spectrum No. 6. IR (KBr) of compound 10d.
Spectrum No. 7. $^1$H NMR (CDCl$_3$) of compound 10d.

Spectrum No. 8. $^{13}$C NMR (CDCl$_3$) of compound 10d.
4.4. EXPERIMENTAL

This part describes the synthetic procedures, spectral and analytical data for all the newly synthesized compounds 10, 11 and 12.

4.4.1. General procedure for the preparation of compound 10, 11 and 12.

A solution of phenyl / ethyl / naphthyl isocyanate/isothiocyanate (0.012 mole) in dry acetonitrile (5 mL) was added slowly to a solution of 1,2,3,4-tetrahydroisoquinoline 7 (0.01 mole) in dry acetonitrile (5 mL). The mixture was stirred at room temperature for 2 h. After the completion (tlc) of the reaction, the separated solid was filtered off and washed with acetonitrile, dried and recrystallized from suitable solvent. The physical and spectral data of compounds are given below.

4.4.2. 1-(6-Methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isooquinoline-2-carbothioic acid phenylamide 10a.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and phenyl isothiocyanate following the general procedure and recrystallizing from ethanol / chloroform (8/2) the product was obtained as a colorless powder. Yield: 100%; m.p. 123-126 °C, IR (KBr): 3375, 3255, 3045, 2920, 2920, 1693, 1595, 1570 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.41 (s, 3H, C₆'-CH₃), 2.96 (m, 1H, C₃-Hₐ), 3.55 (m, 1H, C₄-Hₐ), 3.31 (m, 1H, C₄-Hₐ), 3.80 (m, 1H, <x-H), 4.02 (m, 2H, C₃-Hₐ, a'-H), 5.70 (s, 1H, C₃'-H), 6.48 (m, 1H, C1-H), 6.48-7.38 (m, 12H, Ar-H), 8.31 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): δ 21.2, 28.2, 38.2, 45.0, 60.8, 117.0, 117.0, 119.3, 126.3, 126.6, 126.7, 127.0, 128.1, 128.2, 128.5, 129.2, 129.2, 133.2, 133.8, 134.7, 135.7, 139.9, 151.9, 152.9, 161.1, 182.6; Anal. Calcd. for C₂₉H₂₄N₂O₂S (%); C, 73.61; H, 5.49; N, 6.36; Found; C, 73.77; H, 5.84; N, 6.48.
4.4.3. 1-(6-Methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid phenylamide 10b.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and phenyl isocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 80%, m.p. 143-146 °C, IR (KBr): 3230, 3074, 1719, 1642, 1585 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.39 (s, 3H, C₆'-CH₃), 3.01 (m, 3H, C₃-Hₐ, C₄-Hₐ and C₄-Hₐ'), 3.49 (m, 1H, a-H), 3.75 (m, 2H, C₃-He, a'-H), 5.54 (m, 1H, C₁-H), 6.70 (s, 1H, C₃-H), 6.98-7.37 (m, 13H, Ar-H, NH); Anal. Calcd. for C₂₉H₂₄N₂O₃ (%); C, 76.39; H, 5.70; N, 6.60; Found; C, 76.47; H, 5.84; N, 6.68.

4.4.4. 6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carbothioic acid phenylamide 10c.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and phenyl isothiocyanate following the general procedure and recrystallizing from ethanol/chloroform (8/2) the product was obtained as a colorless powder. Yield: 77%; m.p. 186-188 °C, IR (KBr): 3317, 2988, 2927, 1701, 1609, 1567 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.39 (s, 3H, C₆'-CH₃), 3.01 (m, 2H, C₃-Hₐ, C₄-Hₐ), 3.19 (m, 1H, C₄-Hₐ'), 3.43 (s, 3H, C₆-OCH₃), 3.81 (m, 1H, a-H), 3.87 (s, 3H, C₇-OCH₃), 3.98 (m, 2H, C₃-He, a'-H), 5.90 (s, 1H, C₅-H), 5.99 (s, 1H, C₈-H), 6.38 (m, 1H, C₁-H), 6.72 (s, 1H, C₃-H), 7.2-7.39 (m, 8H, Ar-H), 8.14 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): δ 21.2, 27.8, 38.1, 44.9, 56.2, 56.3, 60.6, 111.1, 111.4, 116.9, 117.0, 119.4, 125.8, 126.4, 126.7, 127.4, 129.3, 129.3, 132.3, 133.3, 134.7, 134.7, 139.9, 147.8, 149.0, 151.9, 153.1, 161.0, 182.6; Anal. Calcd. for C₂₀H₂₈N₂O₄S (%); C, 69.58; H, 5.64; N, 5.60; Found; C, 69.77; H, 5.84; N, 6.68.
4.4.5. 6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isooquinoline-2-carboxylic acid phenylamide 10d.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and phenyl isocyanate following the general procedure and recrystallizing from ethanol / chloroform (8/2) the product was obtained as a colorless powder. Yield: 55%; m.p. 171-173 °C, IR (KBr): 3392, 3252, 3230, 3060, 2922, 1721, 1637, 1595, 1570 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.41 (s, 3H, C₆'-CH₃), 2.95 (m, 1H, C₃-Hₐ), 3.06 (m, 2H, C₄-Hₐ, Hₕ), 3.51 (m, 1H, α-H), 3.59 (s, 3H, C₆-OCH₃), 3.71 (m, 1H, α'-H), 3.87 (s, 3H, C₇-OCH₃), 3.74 (m, 1H, C₃-Hₕ), 5.53 (m, 1H, C₁-H), 5.93 (s, 1H, C₅-H), 6.20 (s, 1H, C₈-H), 6.48 (s, 1H, C₅'-H), 6.68 (s, 1H, C₇'-H), 7.04-7.37 (m, 7H, Ar-H), 7.78 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): δ 21.4, 28.2, 40.0, 41.5, 55.3, 56.3, 56.4, 111.2, 111.5, 116.9, 117.2, 119.2, 120.5, 120.5, 123.7, 125.6, 126.5, 127.9, 129.3, 129.3, 133.2, 134.6, 139.1, 147.8, 148.9, 152.1, 153.0, 155.4, 160.9; Anal. Calcd. for C₂₉H₂₈N₂O₅ (%); C, 71.88; H, 5.82; N, 5.78; Found; C, 71.99; H, 5.94; N, 5.98.

4.4.6. 1-(6-Methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isooquinoline-2-carbothioic acid (4-chloro-phenyl)-amide 10e.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and p-chlorophenyl isothiocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 97%; m.p. 128-130 °C, IR (KBr): 3399, 3029, 2923, 1719, 1618, 1570 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.41 (s, 3H, C₆'-CH₃), 2.93-3.10 (m, 2H, C₃-Hₐ, C₄-He), 3.29 (m, 1H, C₄-Hₐ), 3.78 (m, 1H, α-H), 3.95 (m, 1H, α'-H), 4.04 (m, 1H, C₃-Hₕ), 6.45 (m, 1H, C₁-H), 5.69 (s, 1H, C₃'-H), 6.53-7.43 (m, 11H, Ar-H), 8.23 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): δ 21.2, 28.2, 38.1, 45.0, 60.8, 116.8, 117.0, 119.3, 126.2, 127.0, 127.3, 128.0, 128.2, 128.5, 129.1, 129.1, 130.2, 131.9, 133.3, 133.9, 134.8, 135.2, 138.6, 151.9, 153.1, 161.3, 182.3; Anal. Calcd. for C₂₇H₂₃ClN₂O₂S (%); C, 68.27; H, 4.88; N, 5.90; Found; C, 68.38; H, 4.94; N, 5.98.
4.4.7. 1-(6-Methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid (4-chloro-phenyl)-amide 10f.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and p-chlorophenyl isocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 79%; m.p. 210-213 °C; IR (KBr): 3384, 3360, 3056, 2951, 2925, 1711, 1685, 1595, 1570, 1533 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.45 (s, 3H, C₆'-CH₃), 3.05 (m, 1H, C₃-Hₐ), 3.55 (m, 2H, C₄-Hₐ, C₄'-Hₐ), 3.76 (m, 2H, C₄-Hₐ, C₄'-Hₐ), 3.95 (m, 1H, C₃-Hₐ), 5.58 (s, 1H, C₃'-Hₐ), 5.80 (m, 1H, C₅-Hₐ), 6.79-7.34 (m, 11H, Ar-H), 7.90 (s, 1H, NH); Anal. Calcd. for C₂₇H₂₃ClN₂O₃ (%); C, 70.66; H, 5.05; N, 6.10; Found; C, 70.74; H, 5.15; N, 6.18.

4.4.8. 6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carbothioic acid (4-chloro-phenyl)-amide 10g.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and p-chlorophenyl isothiocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 70%; m.p. 193-195 °C, IR (KBr): 3308, 3055, 2933, 1696, 1604, 1573, 1507 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.39 (s, 3H, C₆'-CH₃), 3.02 (m, 2H, C₃-Hₐ, C₄-Hₐ), 3.23 (m, 1H, C₄-Hₐ), 3.44 (s, 3H, C₆-OCH₃), 3.78 (m, 1H, C₄-Hₐ), 3.87 (s, 3H, C₇-OCH₃), 3.94 (m, 1H, C₆'-Hₐ), 4.01 (m, 1H, C₃-Hₐ), 5.91 (s, 1H, C₅-Hₐ), 6.0 (s, 1H, C₈'-Hₐ), 6.39 (m, 1H, C₁-H), 6.72 (s, 1H, C₃'-Hₐ), 7.16-7.37 (m, 7H, Ar-H), 8.0 (s, 1H, NH); Anal. Calcd. for C₂₉H₂₃ClN₂O₄S (%); C, 70.66; H, 5.09; N, 5.24; Found; C, 65.20; H, 5.25; N, 5.38.
4.4.9. 6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid (4-chloro-phenyl)-amide 10h.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and p-chlorophenyl isocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 72%; m.p. 206-208 °C, IR (KBr): 3361, 3055, 2937, 1654, 1613, 1592 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.39 (s, 3H, C₆'-CH₃), 2.92 (m, 1H, C₃-Hₐ), 3.03 (m, 1H, C₄-Hₐ), 3.50 (m, 1H, C₄-Hₐ), 3.58 (s, 3H, C₆-OCH₃), 3.78 (m, 2H, a-H, a'-H), 3.84 (s, 3H, C₇-OCH₃), 3.85 (m, 1H, C₃-Hₐ), 5.48 (m, 1H, Cl-H), 5.92 (s, 1H, C5-H), 6.19 (s, 1H, C8-H), 6.48 (s, 1H, NH), 6.65 (s, 1H, C3'-H), 7.26-7.73 (m, 7H, Ar-H); Anal. Calcd. for C₂₉H₂₇ClN₂O₅ (%): C, 67.11; H, 5.24; N, 5.40; Found: C, 67.20; H, 5.29; N, 5.48.

4.4.10. 1-(6-Methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carbothioic acid (2,4-difluoro-phenyl)-amide 10i.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and 2,4-difluorophenyl isothiocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 75%; m.p. 150-152 °C, IR (KBr): 3294, 3063, 2930, 1706, 1594, 1515 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.39 (s, 3H, C₆'-CH₃), 2.92-3.11 (m, 2H, C₃-Hₐ, C₄-Hₐ), 3.28 (m, 1H, C₄-Hₐ), 3.78 (m, 1H, a-H), 3.99 (m, 1H, a'-H), 4.04 (m, 1H, C₃-Hₐ), 6.48 (m, 1H, Cl-H), 6.69 (s, 1H, C₃'-H), 6.53-7.43 (m, 10H, Ar-H), 8.23 (s, 1H, NH); Anal. Calcd. for C₂₇H₂₂F₂N₂O₂S (%): C, 68.05; H, 4.65; N, 5.88; Found: C, 68.14; H, 4.79; N, 5.94.
4.4.11. 1-(6-Methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-
isoquinoline-2-carboxylic acid (2,4-difluoro-phenyl)-amide 10j.
Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-
1-ylmethyl)-coumarin-2-one 7a and 2,4-difluorophenyl
isocyanate following the general procedure and
recrystallizing from ethanol the product was obtained as a colorless powder.
Yield: 54%; m.p. 168-170 °C, IR (KBr): 3365, 3067, 3023, 2924, 1705, 1657,
1616, 1515 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.43 (s, 3H, C6'-CH₃), 3.05
(m, 3H, C3-H₆, C4-H₆, C4-H₇), 3.54-3.79 (m, 3H, C3-H₇, α-H, α'-H), 5.58 (m,
1H, C1-H), 6.52 (s, 1H, C3'-H), 6.85-7.87 (m, 9H, Ar-H), 8.0 (s, 1H, NH);
Anal. Calcd. for C₂₇H₂₃F₂N₂O₃ (%); C, 70.43; H, 4.82; N, 6.08; Found; C,
70.54; H, 4.89; N, 6.14.

4.4.12. 6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-
dihydro-1H-isoquinoline-2-carbothioic acid (2,4-difluoro-phenyl)-
amide 10k.
Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-
isoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and
2,4-difluorophenyl isothiocyanate following the general
procedure and recrystallizing from ethanol the product was
obtained as a colorless powder. Yield: 45%; m.p. 190-192 °C, IR (KBr): 3323,
3080, 3005, 2955, 2927, 1711, 1613, 1569, 1546 cm⁻¹; ¹H NMR (300 MHz,
CDCl₃): δ 2.37 (s, 3H, C6'-CH₃), 2.95- 3.05 (m, 2H, C3-H₆, C4-H₆), 3.25 (m,
1H, C4-H₇), 3.42 (m, 1H, α-H), 3.95 (m, 1H, α'-H), 4.08 (m, 1H, C3-H₇), 5.89
(s, 1H, C5-H), 5.98 (s, 1H, C8-H), 6.37 (m, 1H, C1-H), 6.72 (s, 1H, C3'-H),
6.91 (m, 2H, C7', C8'-H), 7.08 (s, 1H, C5'-H), 7.17 (d, 1H, J = 9.0 Hz, C5''-H),
7.31 (d, 1H, J = 9.0 Hz, C6''-H), 7.61 (s, 1H, C3''-H), 8.06 (s, 1H, NH); ¹³C
NMR (75 MHz, CDCl₃): δ 21.2, 27.8, 37.9, 44.9, 56.2, 56.3, 60.9, 104.6,
111.1, 111.4, 111.5, 116.9, 117.0, 117.0, 119.4, 125.7, 126.2, 127.2, 130.6,
133.3, 133.3, 134.7, 134.7, 147.8, 149.1, 151.9, 153.0, 161.0, 182.4; Anal.
Calcd. for C₂₉H₂₆F₂N₂O₄S(%) ; C, 64.91; H, 4.88; N, 5.22 Found; C, 64.98; H,
4.89; N, 5.34.
4.4.13. 6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isooquinoline-2-carboxylic acid (2,4-diflouro-phenyl)-amide 10l.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isooquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and 2,4-difluorophenyl isocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 78%; m.p. 176-179 °C, IR (KBr): 3359, 3209, 3079, 2992, 2919, 1710, 1653, 1613, 1571 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.39 (s, 3H, C₆'-CH₃), 2.90-3.07 (m, 3H, C₃-Hₐ, C₄-Hₐ, Hₐ), 3.49 (m, 1H, a-H), 3.58 (s, 3H, C₆-OCH₃), 3.65-3.76 (m, 2H, C₃-Hₐ, a'-H), 3.65-3.76 (m, 2H, C₃-Hₐ, a'-H), 3.86 (s, 3H, C₇-OCH₃), 5.48 (m, 1H, C₁-H), 5.95 (s, 1H, C₅-H), 6.19 (s, 1H, C₈-H), 6.54 (s, 1H, C₃'-H), 6.68-7.71 (m, 6H, Ar-H), 7.98 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): δ 21.3, 28.1, 39.9, 41.5, 55.4, 56.3, 56.4, 111.2, 111.5, 116.8, 116.9, 117.1, 117.1, 119.3, 125.5, 126.4, 126.4, 127.7, 127.7, 133.2, 133.2, 134.5, 147.8, 148.9, 152.1, 152.9, 154.9, 160.9; Anal. Calcd. for C₂₉H₂₆F₂N₂O₅ (%); C, 66.92; H, 5.03; N, 5.38 Found; C, 66.98; H, 5.10; N, 5.44.

4.4.14. 1-(6-Methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isooquinoline-2-carbothioic acid (4-bromo-phenyl)-amide 10m.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isooquinolin-1-ylmethyl)-coumarin-2-one 7a and 4-bromophenyl isothiocyanate following the general procedure and recrystallizing from ethanol / chloroform (8/2) the product was obtained as a colorless powder. Yield: 100%; m.p. 158-160 °C, IR (KBr): 3262, 3023, 2929, 2852, 1706, 1614, 1569, 1515 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.41 (s, 3H, C₆'-CH₃), 2.96-3.13 (m, 2H, C₃-Hₐ, C₄-Hₐ), 3.33 (m, 1H, C₄-He), 3.79 (m, 1H, a-H), 3.98 (m, 1H, a'-H), 4.06 (m, 1H, C₃-Hₐ), 5.70 (s, 1H, C₃'-H), 6.56-7.5 (m, 11H, Ar-H), 8.27 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): δ 21.2, 28.1, 38.1, 45.1, 60.8, 117.1, 117.1, 119.3, 127.1, 127.1, 128.1, 128.1, 128.1, 128.6, 132.3, 132.3, 133.3, 133.3, 133.6, 134.7, 134.7, 135.1, 138.8, 152.0, 161.5.
152.7, 161.0, 182.6; Anal. Calcd. for C$_{27}$H$_{23}$BrN$_2$O$_2$S (%); C, 62.43; H, 4.46; N, 5.39 Found; C, 62.48; H, 4.59; N, 5.44.

4.4.15. 6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isouquinoline-2-carbothioic acid (4-bromo-phenyl)-amide 10n.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isouquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and 4-bromophenyl isothiocyanate following the general procedure and recrystallizing from ethanol / chloroform (8/2) the product was obtained as a colorless powder. Yield: 86%; m.p. 198-200 °C, IR (KBr): 3305, 3046, 2930, 1696, 1611, 1567, 1515 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 2.39 (s, 3H, C$_6$'-CH$_3$), 3.01 (m, 2H, C$_3$-H$_a$, C$_4$-H$_e$), 3.2 (m, 1H, C$_4$-H$_d$), 3.40 (s, 3H, C$_6$-OCH$_3$), 3.8 (m, 1H, α-H), 3.87 (s, 3H, C$_7$-OCH$_3$), 3.95 (m, 1H, α'-H), 4.01 (m, 1H, C$_3$-H$_e$), 5.91 (s, 1H, C$_5$-H), 6.0 (s, 1H, C$_8$-H), 6.36 (m, 1H, C$_1$-H), 6.72 (s, 1H, C$_3$'-H), 7.11-7.50 (m, 7H, Ar-H), 8.0 (s, 1H, NH); Anal. Calcd. for C$_{27}$H$_{27}$BrN$_2$O$_4$S (%); C, 60.10; H, 4.70; N, 4.83 Found; C, 60.28; H, 4.79; N, 5.84.

4.4.16. 1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isouquinoline-2-carboxylic acid (2-bromo-phenyl)-amide 10o.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isouquinolin-1-ylmethyl)-coumarin-2-one 7a and 2-bromophenyl isocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 53%; m.p. 150-152 °C, IR (KBr): 3416, 3062, 2943, 2909, 2862, 1716, 1665, 1588, 1532 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 2.44 (s, 3H, C$_6$'-CH$_3$), 2.96-3.14 (m, 3H, C$_3$-H$_a$, C$_4$-H$_e$, H$_a$), 3.58 (m, 1H, α-H), 3.67 (m, 1H, α'-H), 3.87 (m, 1H, C$_3$-H$_e$), 5.60 (m, 1H, C$_1$-H), 5.77 (s, 1H, C$_3$'-H), 7.92 (s, 1H, NH), 6.72-8.27 (m, 11H, Ar-H); Anal. Calcd. for C$_{27}$H$_{23}$BrN$_2$O$_3$ (%); C, 64.42; H, 4.61; N, 5.56 Found; C, 64.48; H, 4.75; N, 5.64.
4.4.17. 6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isooquinoline-2-carboxylic acid (2-bromo-phenyl)-amide 10p.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isooquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and 2-bromophenyl isocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 74%; m.p. 128-130 °C, IR (KBr): 3240, 2997, 2924, 1715, 1627, 1573, 1515 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ 2.41 (s, 3H, C6'-CH3), 3.0-3.08 (m, 3H, C3-Ha, C4-Ha, He), 3.52 (m, 1H, α-H), 3.57 (s, 3H, C6-OCH3), 3.65 (m, 1H, C3-Ha), 3.82 (m, 1H, C3-Ha), 3.87 (s, 3H, C7-OCH3), 5.52 (dd, 1H, J = 8.1, 4.8 Hz, C1-H), 5.94 (s, 1H, C5-H), 6.18 (s, 1H, C8-H), 6.70 (s, 1H, C5'-H), 6.93 (t, 1H, J = 7.5 Hz, C4''-H), 7.09 (s, 1H, C5'-H), 7.21 (d, 1H, J = 8.5 Hz, C7'-H), 7.28 (m, 2H, C5'', C3''-H), 7.77 (s, 1H, NH), 8.25 (d, 1H, J = 8.5 Hz, C8'-H); ^13C NMR (75 MHz, CDCl3): δ 21.4, 28.1, 40.0, 41.8, 55.5, 56.3, 111.3, 111.4, 113.7, 116.9, 117.1, 119.4, 121.6, 124.3, 125.7, 126.4, 127.7, 128.8, 132.3, 133.2, 134.5, 137.1, 147.8, 148.9, 152.1, 152.9, 154.7, 160.9; Anal. Calcd. for C29H27BrN2O5 (%); C, 61.82; H, 4.83; N, 4.97 Found; C, 61.98; H, 4.85; N, 5.04.

4.4.18. 1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isooquinoline-2-carboxylic acid (2-chloro-phenyl)-amide 10q.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isooquinolin-1-ylmethyl)-coumarin-2-one 7a and 2-chlorophenyl isocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 53%; m.p. 162-165 °C, IR (KBr): 3427, 3067, 3014, 2921, 2862, 1714, 1660, 1617, 1567, 1531 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ 2.44 (s, 3H, C6'-CH3), 3.04 (m, 3H, C3-Ha, C4-Ha, He), 3.55-3.68 (m, 2H, α-H, α'-H), 3.85 (m, 1H, C3-Ha), 5.59 (m, 1H, C1-H), 5.78 (s, 1H, C3'-H), 6.75-8.27 (m, 11H, Ar-H), 7.93 (s, 1H, NH); Anal. Calcd. for C27H23ClN2O3 (%); C, 70.66; H, 5.05; N, 6.10; Found; C, 70.78; H, 5.15; N, 6.24.
4.4.19. 6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid (2-chloro-phenyl)-amide 10r.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and 2-chlorophenyl isocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 70%; m.p. 123-125 °C, IR (KBr): 3250, 3018, 2925, 1716, 1663, 1628, 1516 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.42 (s, 3H, C6-CH\(_3\)), 2.99-3.08 (m, 3H, C3-H\(_a\), C4-H\(_e\), C6-OCH\(_3\)), 3.53 (m, 1H, \(\alpha\)-H), 3.58 (s, 3H, C6-OCH\(_3\)), 3.66 (m, 1H, \(\alpha\'-H\)), 3.81 (m, 1H, C3-H\(_e\)), 3.88 (s, 3H, C7-OCH\(_3\)), 5.51 (dd, 1H, \(J = 5.1, 3.0\) Hz, C1-H), 5.94 (s, 1H, C5-H), 6.19 (s, 1H, C8-H), 6.70 (s, 1H, C3'-H), 7.78 (s, 1H, NH), 6.97-8.28 (m, 7H, Ar-H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 21.4, 28.1, 40.0, 41.7, 55.5, 56.3, 56.4, 111.2, 111.4, 116.9, 117.2, 119.4, 121.3, 122.8, 123.8, 125.6, 126.4, 127.7, 128.1, 129.1, 133.2, 134.5, 135.9, 147.8, 148.9, 152.1, 152.8, 154.6, 161.0.; Anal. Calcd. for C\(_{29}\)H\(_{27}\)ClN\(_2\)O\(_5\) (%); C, 67.11; H, 5.24; N, 5.40; Found; C, 67.22; H, 5.35; N, 5.54.

4.4.20. 1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carbothioic acid ethylamide 11a.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and Ethyl isothiocyanate following the general procedure and recrystallizing from ethanol / chloroform (8/2) the product was obtained as a colorless powder. Yield: 79%; m.p. 195-197 °C, IR (KBr): 3362, 3026, 2926, 1707, 1616, 1570 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.26 (t, 3H, \(J = 7.2\) Hz, CH\(_2\)CH\(_3\)), 2.44 (s, 3H, C6'-CH\(_3\)), 2.92-3.04 (m, 2H, C3-H\(_e\), C4-H\(_e\)), 3.22-3.31 (m, 1H, C4-H\(_a\)), 3.51 (m, 1H, \(\alpha\)-H), 3.75-3.94 (m, 4H, \(\alpha\'-H\), C3-H\(_e\), CH\(_2\)CH\(_3\)), 5.62 (m, 1H, C1-H), 6.43 (s, 1H, C3'-H), 6.43-7.35 (m, 7H, Ar-H), 8.28 (s, 1H, NH); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 15.0, 21.2, 28.0, 38.4, 41.5, 44.0, 60.5, 116.8, 116.9, 119.4, 126.4, 127.0, 127.9, 128.0, 128.4, 133.2, 133.9, 134.6, 135.6, 151.9, 153.1, 161.1, 181.9.; Anal. Calcd. for C\(_{23}\)H\(_{24}\)N\(_2\)O\(_2\)S (%); C, 70.38; H, 6.16; N, 7.14; Found; C, 70.52; H, 6.25; N, 7.24.
4.4.21. **6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carbothioic acid ethylamide 11b.**

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and Ethyl isothiocyanate following the general procedure and recrystallizing from ethanol / chloroform (8/2) the product was obtained as a colorless powder. Yield: 55%; m.p. 196-198 °C; IR (KBr): 3336, 3061, 2959, 2929, 1711, 1613, 1569, 1543 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.26 (t, 3H, J = 7.2 Hz, CH₂CH₃), 2.40 (s, 3H, C₆'-CH₃), 2.95 (m, 2H, C₃-Hₐ, C₄-Hₜ), 3.15 (m, 1H, C₄-Hₐ), 3.40 (s, 3H, C₆-OCH₃), 3.47 (m, 1H, α-H), 3.74 (m, 1H, α'-H), 3.76 (m, 2H, CH₂CH₃), 3.83 (s, 3H, C₇-OCH₃), 3.88 (m, 1H, C₃-Hₜ), 5.65 (s, 1H, C₃-H), 5.89 (s, 1H, C₅-H), 5.97 (s, 1H, C₈-H), 6.36 (m, 1H, C₁-H), 6.67 (s, 1H, C₅'-H), 7.18 (d, 1H, J = 8.5 Hz, C₇'-H), 7.31 (d, 1H, J = 8.4 Hz, C₈'-H), 8.0 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): δ 15.0, 21.2, 27.7, 38.3, 41.7, 43.9, 56.1, 56.3, 60.4, 111.0, 111.4, 116.8, 119.4, 126.0, 126.4, 127.8, 133.2, 134.6, 147.7, 148.8, 151.9, 153.5, 161.1, 181.7; Anal. Calcd. for C₃₂H₂₃N₂O₄S (%); C, 66.35; H, 6.24; N, 6.19; Found; C, 66.42; H, 6.35; N, 6.24.

4.4.22. **1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carbothioic acid naphthalen-1-ylamide 12a.**

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and 1-Naphthyl isothiocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 94%; m.p. 135-137 °C, IR (KBr): 3326, 3030, 2926, 1721, 1618, 1594, 1570 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.42 (s, 3H, C₆'-CH₃), 2.93 (m, 1H, C₃-Hₐ), 3.07 (m, 1H, C₄-Hₜ), 3.29 (m, 1H, C₄-Hₐ), 3.80 (m, 1H, α-H), 3.96 (m, 1H, α'-H), 4.01 (m, 1H, C₃-Hₜ), 5.65 (s, 1H, C₃'-H), 6.45 (m, 1H, C₁-H), 6.51-7.86 (m, 14H, Ar-H), 8.29 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): δ 21.2, 28.2, 38.2, 60.7, 60.9, 116.9, 116.9, 119.3, 122.9, 125.8, 125.9, 126.4, 126.6, 126.9, 127.0, 128.1, 128.2, 128.5, 128.8, 130.7, 133.2, 133.8, 134.7, 134.7, 135.3, 136.2, 151.9, 153.0, 161.2, 171.5, 183.7; Anal.
Calcd. for C_{31}H_{26}N_{2}O_{2}S (%); C, 75.89; H, 5.34; N, 5.71; Found; C, 75.94; H, 5.45; N, 5.84.

4.4.23. 1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid naphthalen-1-ylamide 12b.

Starting from 6-Methyl-4-(1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-coumarin-2-one 7a and 1-Naphthyl isocyanate following the general procedure and recrystallizing from ethanol the product was obtained as a colorless powder. Yield: 47%; m.p. 148-150 °C, IR (KBr): 3277, 3052, 2924, 1726, 1623, 1570, 1526 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.37 (s, 3H, C₆'-CH₃), 3.06 (m, 3H, C₃-Hₐ, C₄-Hₐ, Hₐ), 3.55 (m, 1H, α-H), 3.74 (m, 1H, α'-H), 3.88 (m, 1H, C₃-He), 5.65 (m, 1H, C₁-H), 5.83 (s, 1H, C₃'-H), 6.75-7.85 (m, 15H, Ar-H, NH); Anal. Calcd. for C_{31}H_{26}N_{2}O_{3} (%); C, 78.46; H, 5.52; N, 5.90; Found; C, 78.54; H, 5.65; N, 5.94.

4.4.24. 6,7-Dimethoxy-1-(6-methyl-2-oxo-2H-chromen-4-ylmethyl)-3,4-dihydro-1H-isoquinoline-2-carbothioic acid naphthalen-1-ylamide 12c.

Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and 1-Naphthyl isothiocyanate following the general procedure and recrystallizing from ethyl acetate / hexane (9/1) the product was obtained as a colorless powder. Yield: 46%; m.p. 167-170 °C; IR (KBr): 3280, 2997, 2926, 1704, 1615, 1570, 1510 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.35 (s, 3H, C₆'-CH₃), 3.0 (m, 1H, C₃-Hₐ), 3.2-3.31 (m, 2H, Ĉ₄-Hₑ, Hₐ), 3.43 (s, 3H, C₆-OCH₃), 3.61 (m, 1H, α-H), 3.75 (m, 1H, α'-H), 3.87 (s, 3H, C₇-OCH₃), 4.0 (m, 1H, C₃-He), 5.9 (s, 1H, C₅-H), 5.98 (s, 1H, C₈-H), 6.41 (m, 1H, C₁-H), 6.71 (s, 1H, C₃'-H), 7.18-7.88 (m, 10H, Ar-H), 8.15 (s, 1H, NH); Anal. Calcd. for C_{33}H_{30}N_{2}O_{4}S (%); C, 71.98; H, 5.49; N, 5.09; Found; C, 71.84; H, 5.65; N, 5.24.
Starting from 4-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)-6-methyl-coumarin-2-one 7b and 1-Naphthyl isocyanate following the general procedure and recrystallizing from alcohol the product was obtained as a colorless powder. Yield: 80%; m.p. 167-170 °C; IR (KBr): 3238, 3048, 2959, 2919, 1717, 1614, 1574, 1516 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.35 (s, 3H, C₆'-CH₃), 3.06 (m, 3H, C₃-Hₐ, C₄-Hₐ, Hₐ), 3.53 (m, 1H, α-H), 3.60 (s, 3H, C₆-OCH₃), 3.75 (m, 1H, α'-H), 3.80 (m, 1H, C₃-Hₐ), 3.89 (s, 3H, C₇-OCH₃), 5.58 (m, 1H, Cl-H), 5.98 (s, 1H, C₅-H), 6.21 (s, 1H, C₈-H), 6.71 (s, 1H, C₃'-H), 6.74-7.86 (m, 11H, Ar-H, NH); Anal. Calcd. for C₃₃H₃₀N₂O₅ (%); C, 74.14; H, 5.66; N, 5.24; Found; C, 74.24; H, 5.75; N, 5.34.

4.5. BIOLOGICAL ACTIVITY

Anti-microbial activity

The test compounds were assayed for anti-microbial activity against *Staphylococcus aureus*, *Streptococcus faecalis*, *Bacillus subtilis* (Gram-positive), and *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginos* (Gram-negative) bacteria and *Saccharomyces cerevisiae* and *Candida albicans* (fungi).

Materials used

1. Nutrient broth
2. Sterile test tubes
3. 24 hours old growth cultures in nutrient broth
4. Sterile pipettes, etc.

Antibacterial assay

The cultures were obtained in Mueller–Hinton broth for all the bacteria after 24 h of incubation at 37 °C. Testing was carried out on Mueller–Hinton broth at pH 7.4 and the two fold serial dilution technique was applied. A set of
tubes containing only inoculated broth was kept as control. After incubation for 24 h at 37°C, the last tube with no growth of microorganism was recorded to represent MIC. Every experiment in the antibacterial assay was replicated twice in order to define the MIC values.

**Antifungal assay**

The *Saccharomyces cerevisiae* and *Candida albicans* were maintained in RPMI 1640 broth. The test procedure was applied according to the NCCLS protocols.21,22 A set of tubes containing only inoculated broth was kept as control. After incubation for 48 h at 35 °C, the last tube with no fungal growth was recorded to represent minimum inhibitory concentration (MIC), expressed in μg/mL. Every experiment in the antifungal assay was replicated twice in order to define the MIC values.

**Method of testing**

The MIC was determined by using two fold serial dilution method23,24 with 96-well micro test plates. Ampicillin, amoxycillin, tetracycline, streptomycin, clotrimazole were used as reference standards to compare the antibacterial and anti-fungal activities, respectively.

For determining both antibacterial and antifungal activities, the synthesized compounds and the control drugs were dissolved in redistilled, dimethyl sulphoxide (DMSO). Further dilutions were prepared at the required quantities of 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1 μg ml⁻¹ respectively.

In order to ensure that the solvent had no effect on bacterial growth, a control test was also performed containing broth supplemented with only DMSO at the same dilution used in our experiment.

The MIC values were obtained from the lowest concentration of the test compound where the tubes remain clear, indicating that the bacterial growth was completely inhibited at this concentration. The results are shown in table 1.
Conclusion

Among all the tested compounds 10e and 10g have shown moderate to good activity against bacterial and fungal strains compared to the standards.

Nevertheless, 10d, 12b, 12c, 12d have also shown good activity against fungal strains compared to standards; all other tested compounds have shown moderate activity against bacterial and fungal strains.

Table No. 1
Anti-microbial activity results (MIC VALUES)

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REFERENCES


