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Synthesis of Indolecarboxamides and Their Docking Studies with H1,5HT and CCR2 Antagonist Receptors

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ABSTRACT

A simple and straightforward novel method to synthesis indolecarboxamides by amidation of indole carboxylic acid and amines in the presence of TCT was developed. The newly synthesized indolecarboxamide ligands 3a-m were subjected to *in silico* docking studies against H1,5HT and CCR2 antagonist receptor. Good to excellent yield of 3a-m was obtained when we use 0.25 equivalent of TCT to couple indole carboxylic acid and amine in THF solvents. This methods was convenient both for aliphatic and aromatic amines. Further this method tolerates different functionality such as hydroxyl, chloro, fluoro and trifluoromethyl as well. *In silico*study reveals that the ligands 3a-m were exhibited good to excellent binding interactions with H1 protein receptor. In particular 3b, 3c & 3i have shown strong 3 hydrogen bonding interaction each with H1 protein receptor whose binding energy is -19.1501, -14.8505, -17.1749 Kcal/mol and inhibitory constant of is 91.6718, 100.49, 85.0736 µM respectively. At the same time the ligands 3a-m have shown moderate inhibition and hydrogen bond interaction with 5HT and CCR2 protein receptors. Here the ligands 3b, 3c & 3i shows single hydrogen bonding interaction with 5HT protein receptor whose binding energies are -10.9311, -9.2191 -11.1749 Kcal/mol respectively is a moderate interaction and thus drawing the attention in terms of high degree of selectivity of the ligands with protein receptors.

Keywords: Indolecarboxamides, TCT, docking, antagonist receptor.

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INTRODUCTION

The 2,4,6-Trichloro-1,3,5-triazine (TCT) is an inexpensive, readily available chemical in the laboratory. This compound was used as a starting material for the synthesis of various heterocycles[1,2]. Recently TCT has served as an inexpensive, nonvolatile, and easy to handle reagent for various organic transformations[3-6].

For instance, TCT promotes Beckman rearrangement[7], sulfide to sulfone oxidation[8], Swern oxidation[9], Lossen rearrangement[10], sulfonyl chloride preparation[11], and Friedel–Craft acylation[12]. TCT is often used for functional group transformations such as carboxylic acid into esters, amides, and peptides[13], and sulfonic acids into sulphonamides[14]. Furthermore, it has been used in the construction of heterocyclic ring like 1,3,4 oxadiazoles[15], 2-aryl benzothiazoles[16], and bisindoles[17] and in the multicomponent reaction[18–20]. TCT is also employed in the solid support reactions[21,22]. Interestingly, in all the above examples the product isolation was easy and yields were ranging from good to excellent.

It was known that about 90% of actual patent applications citing CNS diseases claim serotonergic agents[23]. At least 14 distinct serotonin (5-HT) receptor subclasses are expressed in the mammalian CNS[24]. H1 antagonists are used for the treatment of allergic rhinitis[25]. First-generation H1 antagonists are effective but they cause sedation and dry mouth due to blood–brain barrier and lack of specificity[26], respectively. Whereas second-generation H1 antagonists have low sedative potential although most of them present cardiotoxic side effects. On the other hand the C-C chemokine receptor type 2 is a protein which encodes the Monocyte chemoattractant protein-1 which is involved in monocyte infiltration in inflammatory diseases such as rheumatoid arthritis as well as in the inflammatory response against tumors[27].

The indolecarboxamides structures were found in many biologically active components and for instance they found to be the potent ligand for the treatment of osteroporosis[28]. They also found in Na^+/H^+ exchanger inhibitors[29]. The indolepropanamides were considered to be potent against psoriasis[30] and shown promising potency against murine splenocytes proliferation assay[31].

Encouraged by these results further we also prompted by our earlier work on TCT[32] in the Fischer indole synthesis and *in silico* study[33,34] we applied the TCT for the synthesis of indolecarboxamides using various indole carboxylic acids and amines. Thus we subjected these indolecarboximdes for the docking study to check the *in silico* binding affinity against H1,5HT and CCR2 antagonist receptors.

MATERIALS AND METHOD

Chemistry

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz and 100 MHz Bruker Spectrometer using $CDCl_3$ or DMSO-d_6 solvents and *TMS* as internal standard. Mass spectra were recorded on Agilent 1200 series single quadrapole mass analyzer. Melting points were recorded (uncorrected) in Buchi Melting Point B-545 instrument. The purity of the compounds were checked by TLC and was further purified by column chromatography

Step 1

Synthesis of *N*-(3,4-dichlorobenzyl)-2-(1*H*-indol-3-yl)acetamide 3a

To the solution of indole acetic acid (0.5 g, 2.85 mmol) in anhydrous THF (5mL) was added triethyl amine (0.8 mL, 5.71 mmol) followed by TCT (0.26 g, 1.42 mmol). After 10min was added 4-chloro,3-fluro aniline (0.45 g, 3.13 mmol) at room temperature. After 6 h of strring at room temperature the reaction mass was diluted with water. The product was extracted into ethyl acetate (20 x 3 mL) the organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated to residue. The residue thus obtained was purified by chromatograph to afford the title compound **3a** (yield 0.75 g, 87%).

^{1}H NMR (DMSO-d_6) δ 10.88 (br, 1H), 8.44(t, J = 7.6 Hz, 1H), 7.53 (s, 1H), 7.51 (t, J = 3.6 Hz, 1H), 7.426 (d, J = 1.6, 1H), 7.33(d, J = 8Hz, 1H), 7.20 (dd, J_1 = 2.0 Hz, J_2 = 7.6 Hz, 2H), 7.06(dt, J_1 = 1.2, J_2 = 7.2 Hz, 1H), 6.92(dt, J_1 =0.8 Hz, J_2= 7.2 Hz, 1H), 4.25(d, J = 6, 2H), 3.3(s, 2H) ppm. LCMS: m/z=333.0 (M+1)

Spectral data

***N*-(3,4-dichlorobenzyl)-1*H*-indole-2-carboxamide3h** : ^{1}H NMR (DMSO-d_6) δ 11.62(s, 1H), 9.09(t, J = 6 Hz, 1H), 7.62-7.53(m, 2H), 7.42(d, J = 8Hz, 1H), 7.33(dd, J_1 = 1.6, J_2 = 8.4 Hz, 1H), 7.15-7.16(m, 2H), 7.03(t, J = 7.6 Hz, 1H), 4.01(d, J = 6, 2H), LCMS: m/z=319.0 (M+1).

***N*-cyclohexyl-2-(1*H*-indol-3-yl)acetamide 3f** : ^{1}H NMR (DMSO-d_6) δ 10.83(s, 1H), 7.81(d, J = 8 Hz, 1H), 7.54(d, J = 7.6 Hz, 1H), 7.33(d, J = 8.4 Hz, 1H), 7.15(d, J = 2.4 Hz, 1H), 7.05(dt, J_1 = 0.8 Hz, J_2 = 7.9 Hz, 1H), 6.96(dt, J_1 = 0.84 Hz, J_2 = 7.84 Hz, 1H), 3.55 -3.48(m, 2H), 3.46(s, 1H), 1.72-1.64(m, 4H), 1.53(d, 12.2 Hz, 1H), 1.28-1.09(m, 5H) ppm. LCMS: m/z=257.2 (M+1).

2-(1*H*-indol-3-yl)-1-(4-(trifluoromethyl)piperidin-1-yl)ethanone 3d : ^{1}H NMR (DMSO-d_6) δ 10.9(s,1H), 7.55(d, J = 7.84 Hz, 1H), 7.34(d, J = 8.04 Hz, 1H), 7.20(d, J = 2.04 Hz, 1H), 7.07(t, J = 7.12 Hz, 1H), 6.96(t, J = 7.44 Hz, 1H), 4.51(d, J = 13.08 Hz, 1H), 4.11(d, J = 13.96 Hz, 1H),

3.78(s, 2H), 2.98(t, *J* = 12.56 Hz, 1H), 2.56-2.52(m, 2H), 1.77(d, *J* = 12.44 Hz, 1H), 1.67(d, *J* = 12.44 Hz, 1H), 1.22-1.06(m, 2H) ppm. LCMS: m/z=311.2 (M+1).

***N*-(4-chloro-3-fluorophenyl)-1*H*-indole-7-carboxamide 3c** : ^{1}H NMR (DMSO-d_6) δ 11.27(s, 1H), 10.47(s, 1H), 8.2(dd, J_1 = 2.56 Hz, J_2 = 6.92 Hz, 1H), 7.82(d, *J* = 7.64 Hz, 1H), 7.78-7.74(m, 2H), 7.45(t, *J* = 9.08 Hz, 1H), 7.38(t, *J* = 2.8 Hz, 1H), 7.16(t, *J* = 7.64 Hz, 1H), 6.55-6.53(m, 1H) ppm. LCMS: m/z=287.0 (M+1).

***N*-(4-chloro-3-fluorophenyl)-1*H*-indole-5-carboxamide 3k**: ^{1}H NMR (DMSO-d_6) δ 11.42(s, 1H), 10.31(s, 1H), 8.26(d, *J* = 1.48 Hz, 1H), 8.13(dd, J_1 = 2.50 Hz, J_2 = 6.96 Hz, 1H), 7.78-7.71(m, 2H), 7.51-7.47(m, 2H), 7.41(t, *J* = 9.12 Hz, 1H), 6.60-6.59(m, 1H) ppm. LCMS: m/z=289.0 (M+1).

***N*-(4-chloro-3-fluorophenyl)-1*H*-indole-2-carboxamide3i** : ^{1}H NMR (DMSO-d_6) δ 11.79(s, 1H), 10.39(s, 1H), 8.10(dd, J_1 = 2.56 Hz, J_2 = 6.84 Hz, 1H), 7.78-7.74(m, 1H), 7.69(d, *J* = 7.96 Hz, 1H), 7.48-7.42(m, 3H), 7.24(t, *J* = 8.12 Hz, 1H), 7.08(t, *J* = 7.96 Hz, 1H) ppm. LCMS: m/z=289.4 (M+1).

***N*-(4-chloro-3-fluorophenyl)-2-(1*H*-indol-3-yl)acetamide 3l** : ^{1}H NMR (DMSO-d_6) δ 10.93(s, 1H), 10.31(s, 1H), 7.94(dd, J_1 = 2.52 Hz, J_2 = 6.92 Hz, 1H), 7.58(d, *J* = 7.92 Hz, 1H), 7.51-7.47(m, 1H), 7.38-7.33(m, 1H), 7.26(d, *J* = 2.28 Hz, 1H), 7.07(td, J_1 = 1.08 Hz, J_2 = 8.12 Hz, 1H), 6.98(td, *J*1 = 1.2 Hz, *J*2 = 7.96 Hz, 1H), 3.73(s, 2H) ppm. LCMS: m/z=301. (M-1).

***In silico* molecular docking studies**

Selection of target protein

H1 antihistamines, CCR2 antagonists and 5HT-antagonists protein structures were retrieved from PDB database. Serotonin 5HT receptors complex with cytochrome-b with 3D structure (PDBID: 4IAR) shows antipsychotics propertiy. Histamine H(1) receptor antagonists protein (PDB ID: 3RZE) structure is effective on allergic reactions, Chemokine receptor type 2 (CCR2) proteins play an important role in inflammatory reactions and cognitive function in immune system (PDB ID: 1KAD) and these proteins were potentially targeted for binding with different indolecarboxamides.

Identification of protein structure:

The docking study was performed using AutoDockTools (ADT) v 1.5.4 and AutoDock v 4.2 program to create grid maps of different grid points for covering ligand binding pockets such as active site amino acids. Using molecular modeling and simulation algorithms such as Lamarckian genetic algorithm helps for molecular simulation and docking. Different molecular simulation parameters were used in grid point such as 80 x 80 x 80 and docking. The parameters

such as population size of 150, the mutation rate of 0.02 and crossover rate of 0.8 were fixed accordingly. Secondly, the simulations were performed up to 2.5 million energy and the evaluations were maximum at 27000 generations. Each simulation was carried about 10 times which ultimately yielded 10 docked conformations. From this, the lowest energy conformations were regarded as the best binding conformations. In the end, the reverse validation processes ensured the identified hits that fitted with generated pharmacophore models and active sites of both targets. Since all the parameters were required for molecular docking and pharmacophore mapping, they were consequently fixed and used in the regular process.

RESULTS AND DISCUSSION

Initially in order to check the feasibility of the reaction, the mixture of indole acetic acid and TCT was taken in anhydrous ACN to stir to form acid TCT adduct. Latet after 30 min of strring at room temperature the adduct was treated with 3,4dichloro benzyl amine. To our delight, after 6 h of stirring at room temperature the crude reaction mixture shows new spot as monitored by TLC. The LCMS spectrum confirms that the new spot was the desired amide product. However in this case ,though we found new spot as desired amide product the percentage conversion was not desirable. Hence we attempted several reaction trials to get best result. However when we try to heat the above reaction mixture, more impurities were formed and also observed that the product concentration was decreased. Henceforth we decided to optimize the reaction at room temperature. Thus we varied the catalyst concentration and solvent as well at room temperature for optimization.

The details of the trails carried out are given in the table 1. Accordingly, the best result was obtained when we used 0.5 equiv. of TCT in THF solvent at room temperature. In the case of EtOH solvent no product formation was observed was attributed to the quenching of catalyst by EtOH to liberate HCl gas. When we use less polar solvents the yields was found to reduced drastically. Based on the above optimized condition we carried out remaining reaction to prepare indolecarboxamides**3a-m (**Table 2).

Table 1: Effect of solvent and catalyst concentration on the reaction rate at room temperature 25^0 C

Solvent	Catalystconcentration (TCT) in equiv.	Time in h	% Yield[a]
THF	1	6	83
Dioxane	1	8	60
Toulene	1	10	70
DCM	1	12	40

ACN	1	8	80
EtOH	1	12	0[b]
THF	0.5	6	85

[a]Yields are based on LC/MS, [b] only reactants were observed

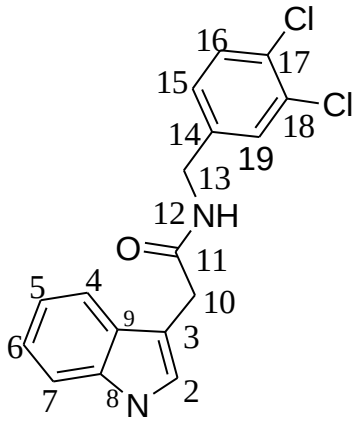
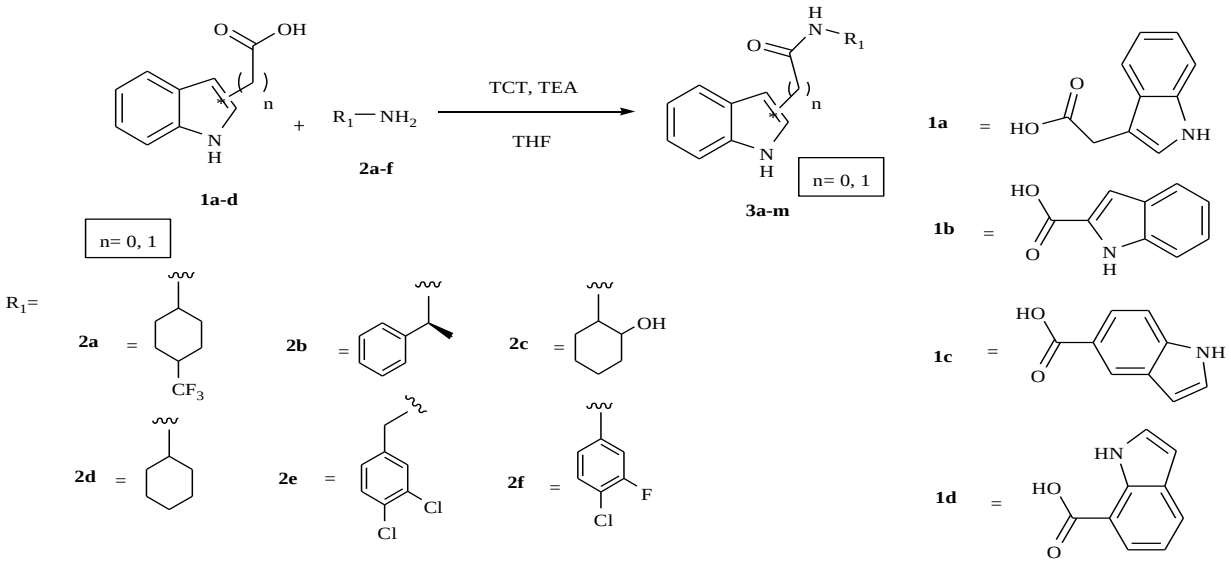
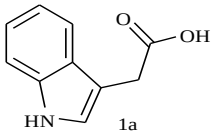
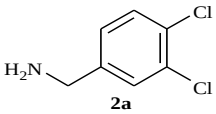
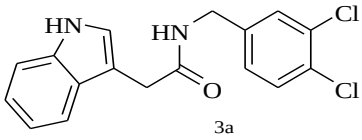
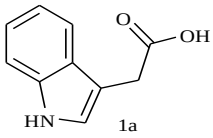
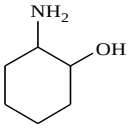
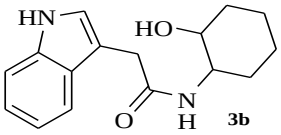
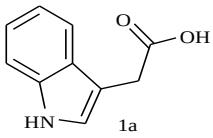
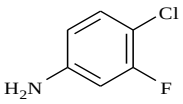
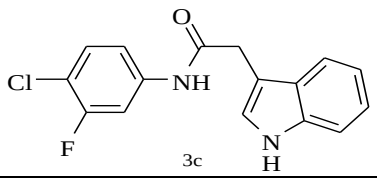
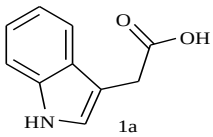
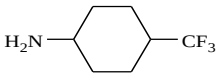
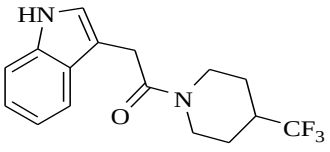
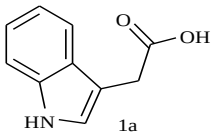
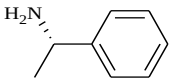
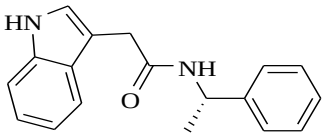
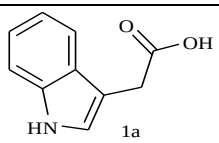
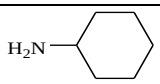
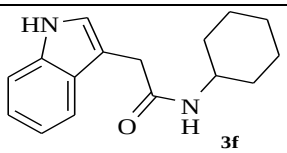
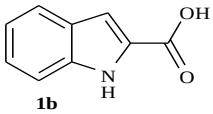
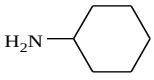
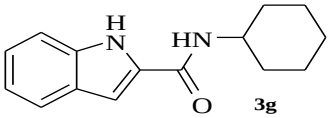
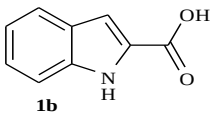
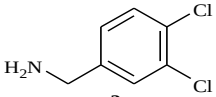
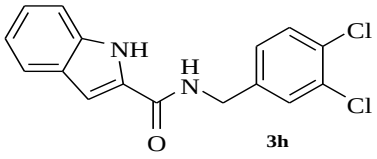
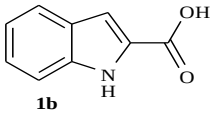
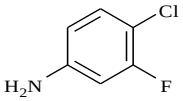
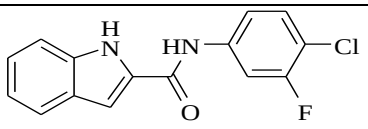
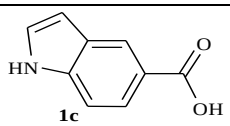
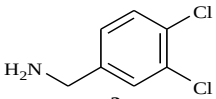
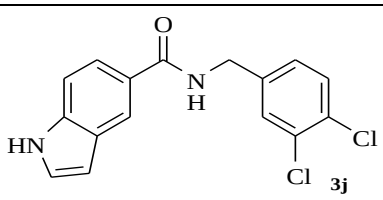


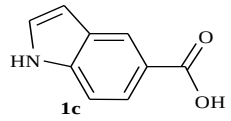
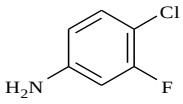
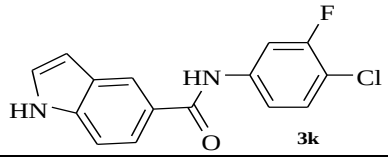
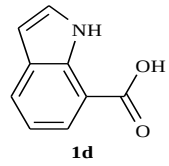
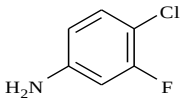
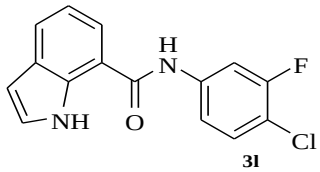
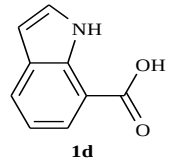
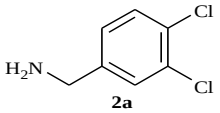
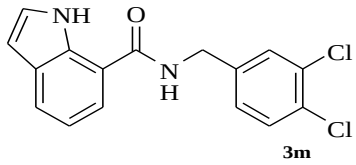
Figure 1: N-(3,4-dichlorobenzyl)-2(1H-indol-3-yl)acetamide 3a

The structure of the indolecarboxamide**3a** was determind by ^{1}H NMR and LC/MS spectral analysis the ^{1}H NMR shows a singlet peak at δ= 3.57 which corresponds to C-10 proton , the doublet at δ= 4.24 which has coupling constant of 6 Hz corresponds to benzylic C-13 proton. This splitting is due to neighbouring amide NH. The peaks in the ranget δ= 6.94-7.53 corresponds to eight aromatic protons. The amide NH appeared as triplet at δ= 8.44. Finally the peak at δ= 10.88 corresponds to indole NH. The structure was further established by LC/MS spectrum of **3a.** It has apeak at 333.2 which corresponds to at [molecular ion+1]. Similarly the structures of all the remaining indolepropamides**3b-m** derivatives were determined.

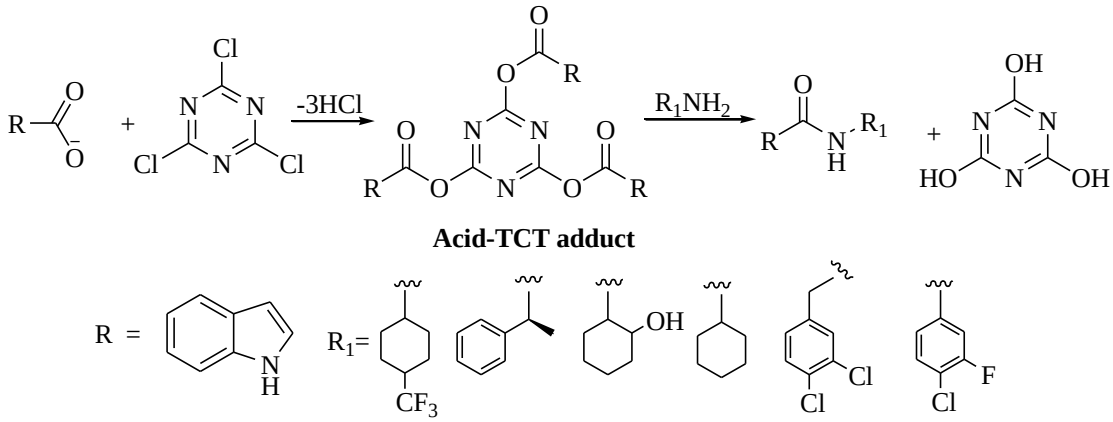
Table 2: General method of synthesis of indolecarboxamides 3a-m using TCT catalyst.



Acid	Amines	Ligands	Yield	MP °C
 1a	 2a	 3a	87	140
 1a	 2b	 3b	84.5	210
 1a	 2c	 3c	85	183
 1a	 2d	 3d	89	160
 1a	 2e	 3e	86	196
 1a	 2f	 3f	86.5	200
 1b	 2f	 3g	84.5	169
 1b	 2a	 3h	88.5	224
 1b	 2c	 3i	90	242
 1c	 2a	 3j	90.5	195

 1c	 2c	 3k	87	240
 1d	 2c	 3l	90	215
 1d	 2a	 3m	86	228

It has been noticed that the TCT promotes the amidation reaction by acid and amine coupling via formation of indole carboxylic acid-TCT adduct in which trizine part acts as good leaving group. This was happen when carboxylate anion attacks the TCT to displace the chloride to form acid-TCT adduct. The acid-TCT adduct enables the nucleophilic attract of amines at the carbonyl carbon of the acid to furnish the desired product (**Scheme 1**). It was further confirmed that when we use EtOH as solvent no product formation was observed[32].



Scheme 1 The Mechanism of formation of amides in the presence of TCT catalyst

Molecular docking sstudies

The molecular analysis of indolecarboxamides with H1, CCR2, 5HT functional protein shows various kinds of interaction such as H-bonding and electrostatic interaction vanderwals bonding. Among the proteins the ligands **3a-m** shows strong interaction with H1 protein and least interaction with CCR2 protein. However with 5HT protein it shows moderate interaction. Particularly the ligands **3b**, **3c**&**3i** shows strong 3 hydrogen bonds each with H1 protein receptor whose binding energy is -19.1501, -14.8505, -17.1749 kcal/mol and inhibitory constant of is 91.6718, 100.49, 85.0736 µM respectively at active site amino acid ASN443, ARG176, and ILE

438 in H1 protein. Relatively similar readings interactions were also observed for **3l, 3m** ligands. However the ligands **3d, 3h**, **3j**, **3k** shows two H-bond interaction with binding energy -12.6387, -11.0597,-9.4869 and -12.0047 kcal/mol respectively implies that these ligands have moderate interaction. Remaining ligands **3a** and **3e** exhibits least interaction with only one Hydrogen bond. The detailed interaction are given in the table 3.

However with the protein receptor 5HT all the ligands shows only one H-bond interaction which is not sufficient enough for protein inhibition with moderate binding energy ranging between -6.8374 to -17.1749 kcal/mol and inhibitory constant ranging 58.875 to 95.5931 µM. Nevertheless the ligands **3h** has two H-bond interaction with binding energy -11.0597 kcal/mol. The detailed data are given in table 4. On the other hand **3a** have no H-bonding interaction and ligand **3b** and **3c** have one H-bonding interaction with binding energy -4.0648, -32.9526 kcal/mol respectively with CCR2 protein receptor. The details are given in the table 5.

Table 3: Docking studies for 5HT protein receptor

Ligand	No. of H-bonds	Binding Energy	Inhibitory_ Const.	Electrostatic_ Energy	Amino acids
3a	1	-9.92288	86.1065	-0.5536	VAL344,
3b	1	-10.9311	67.6697	-3.7477	ALA129,
3c	1	-9.2191	59.8518	-0.3625	ARG152
3d	1	-12.6387	90.0476	-2.0956	TYR215
3e	1	-.6.8374	70.3462	-5.9437	LYS1104
3f	1	-9.7946	71.9052	-6.1753	TYR309
3g	1	-10.6547	73.2809	-3.092	GLU309
3h	2	-11.0597	60.9564	-2.983	TYR228
3i	1	-11.1749	85.0736	-3.1178	TYR215
3j	1	-9.4869	80.3962	-1.9032	THR188
3k	1	-12.0047	78.3548	-3.352	TYR228
3l	1	-8.2487	58.875	-3.972	ALA129
3m	1	-8.9362	95.5931	-2.765	ARG152

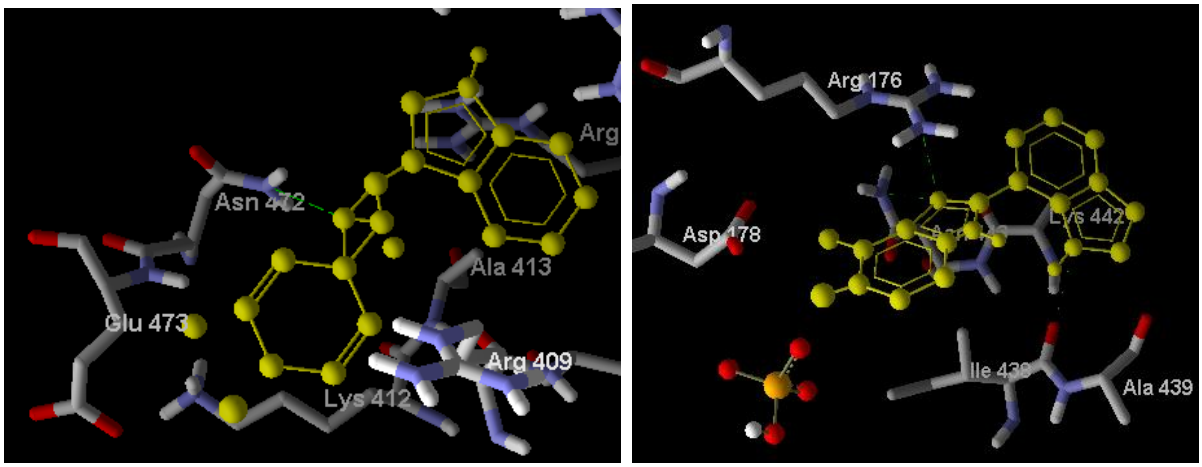
Table 4: Docking studies for H1 protein receptor

Ligand	No. of H-bonds	Binding Energy	Inhibitory_ Const.	Electrostatic Energy	Amino acids
3a	1	-9.93206	81.5372	-2.49944	ASN472
3b	3	-19.1501	91.6718	-2.3727	ASN443, ARG176
3c	3	-14.8505	100.49	-1.70277	ASN443, ILE438, ARG176
3d	2	-12.6387	90.0476	-2.0956	ASN198,LYS179
3e	1	-.6.8374	70.3462	-5.9437	TRP93
3f	1	-9.7946	71.9052	-6.1753	ARG176
3g	1	-10.6547	73.2809	-3.092	ASN472
3h	2	-11.0597	60.9564	-2.983	TRP93,ARG176
3i	3	-17.1749	85.0736	-3.1178	ASN443, ARG176
3j	2	-9.4869	80.3962	-1.9032	TYR431, ARG175

3k	2	-12.0047	78.3548	-3.352	TRP93, ARG176
3l	3	-18.2487	98.875	-3.972	ARG176,ILE438,ASN443
3m	3	-18.9362	95.5931	-2.765	LYS179

Table 5: Docking studies for CCR2 protein receptor

Ligand	No. of H-bonds	Binding Energy	Inhibitory_ Const.	Electrostatic_ Energy	Amino acids
3a	0	--	--	--	---
3b	1	-4.04648	60.9971	-0.7990	ALA145
3c	1	-32.9526	48.4138	-2.43717	GLN354



3c **3l**

Figure 2: Docking images and interaction of 3c and 3l with H1 protein shows 3 hydrogen bonds at amino acid ASN443, ILE438, ARG176

CONCLUSION

We have developed more efficient and high yielding protocol for the synthesis of indolecarboxamides using TCT as catalyst. Both aliphatic and aromatic amine **2a-f** reacted efficiently with indole carboxylic acids **1a-d** to give corresponding indolecarboxamids**3a-m** in good yields**.** Further it was noticed that the method was tolerates wider functionality such as hydroxyl, chloro and fluoro in the reactant hence any number of indolecarboxyamides can be made. Since some of the synthesized indolecarboxamides have shown excellent binding interaction and inhibition activity with H1 protein receptor, these results can be considered for the next level to find out relevant lead development. However the same indolecarboxamides**3a-m** shows moderate to least interaction with both 5HT and CCR2 protein receptor. On similar lines we can further conclude these ligands are selectively binding to H1 and not with 5HT or CCR2 protein receptors. Hence all these results could provide structural information for inhibition activity with H1 protein receptor and improve the understanding of ligand–receptor

interactions. These results may provide some useful and rational suggestions for further design of novel inhibitors for H1 protein receptor.

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