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# Design, synthesis, and biological evaluation of oxindole derivatives as antidepressive agents

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ABSTRACT

The 3-substituted oxindole derivatives were designed, synthesized, and evaluated for antidepressant activity by employing forced swimming test, tail suspension test, and MAO-A inhibition assay. Results of biological studies revealed that the majority of compounds exhibited potent to moderately potent activity and among them, **12** displayed potency comparable to that of the imipramine with %DID of 37.95 and 44.84 in the FST and TST, respectively. At the same time, imipramine showed %DID of 43.62 and 50.64 in the FST and TST, correspondingly. In the MAO-A inhibition assay, **12** showed an $IC_{50}$ of 18.27 μmol, whereas the reference drug moclobemide displayed an $IC_{50}$ of 13.1 μmol. The SAR study disclosed that the presence of bromo atom at the phenyl/furanyl or thienyl moiety in the oxindole derivatives was critical for the antidepressant activity.



According to the World Health Organization, major depression will become the second leading cause of death by the year 2020 because of the complications arising from cardiovascular system and stress.[1] There is a tremendous unmet need for new, safer, and more effective antidepressant drugs, since currently used antidepressants have significant side effects and about 30% of the population does not respond to these current treatments.[2,3] Monoamine oxidase (EC 1.4.3.4, MAO) is an integral protein of the outer mitochondrial membrane, catalyses the oxidative deamination reaction of neurotransmitters such as dopamine, norepinephrine, and serotonin monoamines in central nervous system and peripheral tissues.[4,5] Both the MAO-A and -B are present in the majority of brain areas[6] and have attracted considerable interest because of their key roles in monoamine neurotransmitter metabolism and involvement in various neuropsychiatric disorders.[7] The MAO reaction yields aldehydes and hydrogen peroxide ($H_2O_2$), which induces apoptosis.[8] The inhibition of MAO and subsequent $H_2O_2$ generation effectively prevents depression and various oxidative stresses in the brain.[9] However, classical MAO inhibitors have been shown to have side-effects.[10,11]

Indoles, oxindoles, and isatins (2,3-dioxindoles) are nitrogen-containing heterocyclic compounds, widely distributed in the living world and in its chemical environment. Some indole amines, such as tryptamine and serotonin (Fig. 1) are the substrates of MAO. A recent study revealed that 5-hydroxyisatin selectively inhibits MAO-A, while indole and other isatin analogs were less potent inhibitors of MAO-A and -B.[12] Audia et al. reported affinity of indole derivatives toward $5HT_{2A}$, $5HT_{2B}$, and $5HT_{2C}$ receptors, which could be useful in the treatment of various disorders associated with these receptors, like migraine, anxiety, depression, schizophrenia, tachygastria, ichlasia, and dyspepsia.[13] Furthermore, indole moiety is present in a number of drugs currently in the market and most of these belong to triptans, used for the treatment of migraine headaches. Few of the new molecules reported in the past few years sharing structure similarities with indole moiety are the Wyeth's compounds WAY-161503 and WAY-163909 (Fig. 2), both selective $5HT_{2C}$ receptor agonists, claimed to be useful for the prevention and treatment of depressive disorders.[14–18] A new drug PD-6735 (Fig. 2) too bears an indole moiety in its structure is a melatonin receptor agonist that has recently completed

*Abbreviations:* MAO, monoamine oxidase; FAD, flavin-adenine dinucleotide; FST, forced swimming test; TST, tail suspension test; %DID, percentage decrease in immobility duration; PDB, protein data bank.

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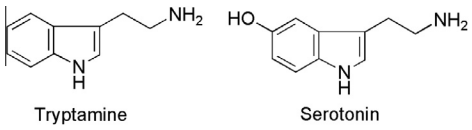



**Figure 1.** Chemical structures of indole amines.

phase II clinical trials for treating sleep disorders in blind individuals.[3] Oxindole is a neurodepressant tryptophan metabolite physiologically present in mammalian brain and blood, and affects brain functions.[19–21] Like indole, several oxindole derivatives have also been reported to possess antidepressant activity.[3]

Relying on the notion that some of the indole and oxindole derivatives share structural similarity with neurotransmitters and endogenous amines,[3] such as MAO substrates serotonin and tryptamine;[22] we thought to synthesize oxindole derivatives as possible antidepressants. Moreover, QSAR and in vitro study performed by Chimenti et al. revealed that chalcones are valid scaffolds for the inhibition of MAO.[23] In this study, some of the chalcones showed a very high selectivity index when compared to the standard antidepressants clorgyline, deprenyl, iproniazid, and moclobemide. Based on this perception, we decided to synthesize derivatives of oxindoles in the form of chalcones. The synthesized compounds were studied for antidepressant activity by employing Porsolt's forced swimming test (FST),[24,25] tail suspension test (TST),[26] and MAO-A inhibition assay.

The title compounds (**3**–**20**) were synthesized by Claisen–Schmidt condensation reaction of a ketone with various aldehydes. The commercially available oxindole (indolin-2-one) (**1**) was stirred with appropriate aldehydes (**2**) in the presence of alcoholic NaOH to afford 3-substituted oxindole derivatives (**3**–**20**) (Scheme 1). All the compounds were obtained in excellent yield (>81%) and their synthesis was confirmed by UV, IR, $^1$H NMR, and mass spectroscopic techniques. The UV spectra of final compounds (**3**–**20**) showed two typical chalcone bands between 312.60–368.40 nm (band-I) and 240.80–258.20 nm (band-II). The IR spectra of compounds (**3**–**20**) exhibited peaks at 3138.26–3186.51, 1690.14–1712.85, and 1587.47–1622.19 cm$^{-1}$ characteristic to the N—H, C=O, and C=C groups of compounds, respectively. The $^1$H NMR spectra of synthesized products revealed that the number of protons were consistent with the proposed structures. All the synthesized products showed two singlets at 7.222–7.755 ppm (1H) and 10.481–10.673 ppm (1H) distinctive to the =CH and NH fragments of the compounds, respectively. Thus, synthesis of α,β-unsaturated carbonyl compounds, that is chalcones (3-substituted oxindoles) was confirmed by the presence of IR and NMR peaks distinctive to the α,β-unsaturated bond and carbonyl group, along with the presence of molecular ion peaks respective to the molecular weights of the synthesized compounds.

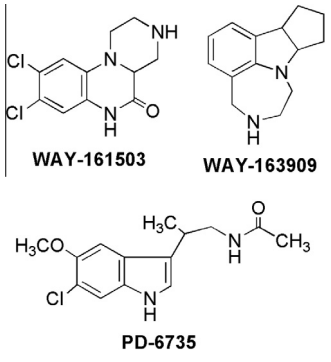
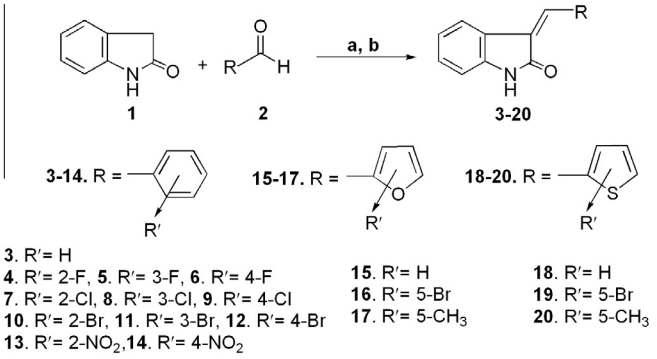



**Figure 2.** Indole and related derivatives under development for depressive (WAY-161503 and WAY-163909) and sleep disorders (PD-6735).




**Scheme 1.** Synthesis of oxindole derivatives (**3**–**20**): (a) alcoholic NaOH; (b) stir 2 h.

FST and TST are the most common animal models of antidepressant drug screening. Both tests are based on the same principle of measurement of the duration of immobility when rodents are exposed to an inescapable situation. Testing of new substances in above tests allows a simple assessment of their potential antidepressant activity by measurement of their effect on immobility. In a comparative review of drug effects on immobility time in mice, Borsini and Meli adopted a limit of 20% reduction of immobility to consider drug as an effective antidepressant.[27] Coming to our experimental setup, Swiss strain of albino mice was chosen because it is sensitive against almost all types of mechanisms involved in the depression,[28,29] and it is an economical option also. The original description of the FST by Porsolt et al.[24] explains that 6 cm of water is sufficient; though, mice can sense the bottom of the cylinder with this level of water. Thus, we performed FST at 10 cm of water level.[30] Hypothermic exposure in FST may be problematic, especially if a targeted gene is involved in thermoregulatory processes.[31] Also, selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline),[32] and drugs enhancing motor activity may give false positive effects in FST. Therefore, we thought to perform; TST parallel with FST to minimize the false positive results. The TST is a dry land version of the FST[29] and it is based on the observation that rodents after initial escape-oriented movements develop an immobile posture when placed in an inescapable stressful situation. In case of the TST, stressful situation involves the hemodynamic stress of being hung in an uncontrollable fashion by their tail. An obvious advantage of this test is its ability to detect a broad spectrum of antidepressants irrespective of their mechanisms and it is inexpensive, methodologically unsophisticated, and easily amenable to automation.[29]

All the synthesized 3-substituted oxindole derivatives (**3**–**20**) were tested in vivo for antidepressant activity employing FST and TST models. Imipramine was used as the standard drug. Results are expressed as immobility time in seconds and percentage decrease in immobility duration (%DID) (Tables 1, 2 and Figs. 3, 4). As listed in Tables 1 and 2, bromo substituted compounds demonstrated higher activity than compounds substituted with other groups at the analogous positions. The compounds **9**, **11**, **12**, and **19** with 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, and 5-bromothienyl substitutions showed promising activity in both the test models with compound **12** exhibiting the highest %DID of 37.95 and 44.84, in the FST and TST, respectively. The compound **9** showed %DID of 36.43 and 44.09, whereas the reference drug imipramine displayed %DID of 43.62 and 50.64 in the FST and TST, respectively. The compounds bearing 3-phenyl ring (**3**–**14**) were more active than the compounds bearing 3-thienyl ring (**18**–**20**), while compounds possessing 3-furanyl ring (**15**–**17**) were least active. The position of groups on the phenyl ring exerted

**Table 1**
Antidepressant activity of test compounds and imipramine in the forced swimming test

| Compound | Dose (mg/kg) | Immobility time (s) mean ± SEM | % immobility | %Decrease in immobility duration (%DID) |
|---|---|---|---|---|
| **3** | 100 | 120.6 ± 2.9*** | 79.44 | 20.56 |
| **4** | 100 | 137.3 ± 2.4* | 90.44 | 09.56 |
| **5** | 100 | 130.8 ± 2.1*** | 86.16 | 13.84 |
| **6** | 100 | 127.9 ± 2.5*** | 84.25 | 15.75 |
| **7** | 100 | 112.6 ± 4.0**** | 74.17 | 25.83 |
| **8** | 100 | 104.8 ± 3.2*** | 69.03 | 30.97 |
| **9** | 100 | 96.5 ± 2.9*** | 63.57 | 36.43 |
| **10** | 100 | 111.4 ± 2.3*** | 73.38 | 26.62 |
| **11** | 100 | 99.7 ± 2.4*** | 65.67 | 34.33 |
| **12** | 100 | 94.2 ± 3.4*** | 62.05 | 37.95 |
| **13** | 100 | 146.9 ± 2.8ns | 96.77 | 03.23 |
| **14** | 100 | 145.2 ± 2.9ns | 95.65 | 04.35 |
| **15** | 100 | 138.8 ± 1.5ns | 91.43 | 08.57 |
| **16** | 100 | 114.9 ± 1.9*** | 75.69 | 24.31 |
| **17** | 100 | 125.6 ± 2.8*** | 82.74 | 17.26 |
| **18** | 100 | 124.6 ± 3.1*** | 82.08 | 17.92 |
| **19** | 100 | 100.9 ± 2.4*** | 66.46 | 33.54 |
| **20** | 100 | 108.2 ± 2.5*** | 71.27 | 28.73 |
| Imipramine | 10 | 85.6 ± 2.3*** | 56.38 | 43.62 |
| Control | — | 151.8 ± 2.1 | 100.00 | — |

$n = 6$. Test compounds and imipramine (reference) were administered orally, 60 min before the test. $^{***}P < 0.00$, $^{**}P < 0.01$, $^{*}P < 0.05$, ns: not significant versus control. Data were analyzed by one way ANOVA followed by Tukey's test.

an important effect on the pharmacological activity. The substituents present at the 4-position of phenyl ring imparted highest activity followed by the substituents present at the 3-position of the phenyl ring. The introduction of substituent on the 2-position of phenyl ring resulted in decreased activity. The size of the substituent also affected the activity. Substitution of bromo group imparted superior activity than activity imparted by chloro and fluoro substitutions present at the analogous positions. Substitution of the nitro group on the phenyl ring caused a dramatic loss of activity. Compounds bearing 3-furanyl ring produced inactive compound (**15**), while substitution of 5-methylfuranyl ring increased the activity, which was further enhanced, when furanyl ring was substituted with 5-bromo group. The activity pattern of furanyl substituted compounds was also repeated in the thienyl substituted compounds, wherein activity order observed was: 5-bromothienyl substitution > 5-methylthienyl substitution > thienyl substitution. Based upon above findings, one can conclude that compounds possessing bromo group demonstrated superior antidepressant activity.

**Table 2**
Antidepressant activity of test compounds and imipramine in the tail suspension test

| Compound | Dose (mg/kg) | Immobility time (s) mean ± SEM | % Immobility | %Decrease in immobility duration (%DID) |
|---|---|---|---|---|
| **3** | 100 | 102.3 ± 1.6*** | 76.05 | 23.95 |
| **4** | 100 | 115.3 ± 2.8*** | 85.72 | 14.28 |
| **5** | 100 | 114.5 ± 1.9*** | 85.13 | 14.87 |
| **6** | 100 | 113.4 ± 2.5*** | 84.31 | 15.69 |
| **7** | 100 | 93.0 ± 2.2*** | 69.14 | 30.86 |
| **8** | 100 | 81.9 ± 1.9*** | 60.89 | 39.11 |
| **9** | 100 | 75.2 ± 2.9*** | 55.91 | 44.09 |
| **10** | 100 | 91.6 ± 2.4*** | 68.10 | 31.90 |
| **11** | 100 | 76.8 ± 2.5*** | 57.10 | 42.90 |
| **12** | 100 | 74.2 ± 3.8*** | 55.16 | 44.84 |
| **13** | 100 | 124.7 ± 3.1ns | 92.71 | 07.29 |
| **14** | 100 | 120.5 ± 2.2* | 89.59 | 10.41 |
| **15** | 100 | 119.7 ± 2.1** | 88.99 | 11.01 |
| **16** | 100 | 95.8 ± 2.7*** | 71.22 | 28.78 |
| **17** | 100 | 109.6 ± 2.8*** | 81.48 | 18.52 |
| **18** | 100 | 107.1 ± 1.6*** | 79.62 | 20.38 |
| **19** | 100 | 78.7 ± 1.1*** | 58.51 | 41.49 |
| **20** | 100 | 88.4 ± 1.9*** | 65.72 | 34.28 |
| Imipramine | 10 | 66.4 ± 2.7*** | 49.36 | 50.64 |
| Control | — | 134.5 ± 3.1 | 100 | — |

$n = 6$. Test compounds and imipramine (reference) were administered orally, 60 min before the test. $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$, ns: not significant versus control. Data were analyzed by one way ANOVA followed by Tukey's test.

Based on the results obtained in the FST and TST models, the most active compounds **9**, **11**, **12**, and **19** those showed immobility time 100 or less seconds, were further studied to find out their activity against MAO-A and compare it against the clinically used drugs moclobemide and clorgyline. The outcome of test compounds **9**, **11**, **12**, and **19** against the bovine MAO-A is presented in Table 3. The 4-bromophenyl substituted oxindole derivative **12** displayed the highest inhibition of MAO-A activity with an $IC_{50}$ of 18.27 μmol. Other bromo group bearing compounds **11** (3-bromophenyl) and **19** (5-bromothienyl) also showed encouraging $IC_{50}$s of 27.2 and 35.1 μmol, respectively against MAO-A. Along with these compounds, another promising lead compound **9** that has 4-chlorophenyl moiety in its structure also exhibited the noteworthy $IC_{50}$ of 29.5 μmol against the MAO-A. Interestingly, the potency of our test compound **12** was similar to that of the clinically used reversible MAO-A inhibitor moclobemide. However, another clinically used irreversible and selective MAO-A inhibitor clorgyline exhibited activity far superior to our test compounds with an $IC_{50}$ of 3.65 nmol against MAO-A. Relying on these preliminary results against bovine MAO-A, we can propose that the test compound **12** is a potential antidepressant that warrants further explorations.

All the eighteen compounds were docked into the active site of human MAO-A using Autodock tools 1.5.4. Results of molecular docking studies are expressed in terms of estimated free energy of binding (kcal/mol). The estimated free energy of binding of all the docked eighteen molecules ranged between −4.95 and −3.69 kcal/mol and is presented in Table 4. The docked complexes of ligands (**3**–**20**) within the active site of MAO-A revealed that the secondary amine (—NH—) and carbonyl (C=O) groups of synthesized derivatives were involved in hydrogen bonding with the Asn-181, Tyr-407, and Tyr-444 residues of the MAO-A. The most active compound (**12**) of in vivo study showed lowest estimated free energy of binding (−4.95 kcal/mol). The hydrogen atom of a secondary amine group of **12** was involved in hydrogen bond formations with the Tyr-444 of MAO-A (N—H···O—H: 1.941 Å) (Figs. 5

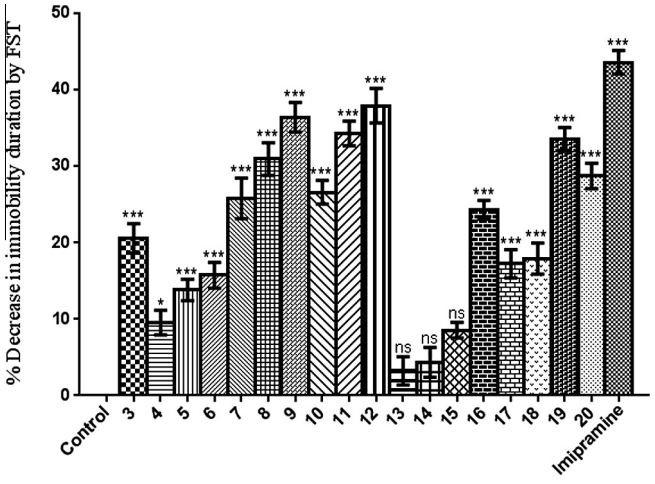



**Figure 3.** Percentage decrease in immobility duration by force swimming test. All the data are mean ± SEM of six mice. $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$, ns: not significant versus control.

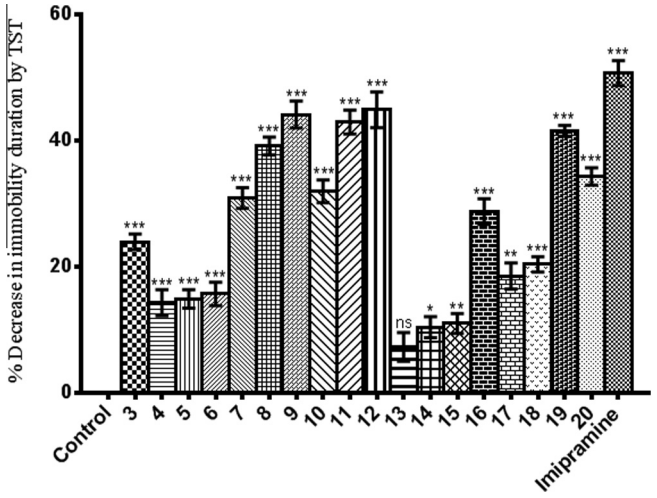



**Figure 4.** Percentage decrease in immobility duration by tail suspension test. All the data are mean ± SEM of six mice. $^{***}P$ <0.001, $^{**}P$ <0.01, $^{*}P$ <0.05, ns: not significant versus control.

and 6) and at the same time, a nitrogen atom of secondary amine was 2.654 Å away from the hydroxyl hydrogen of the Tyr-444. The distance between the carbonyl group of **12** and Asn-181 was found to be 5.032 Å. Apart from hydrogen bonding, 4-bromophenyl portion of the lead compound **12** displayed strong hydrophobic and van der Waals interactions with the Phe-177, Ile-180, Phe-208, and Ile-335 residues of the MAO-A. Additionally, oxindole scaffold of **12** demonstrated hydrophobic and van der Waals interactions with the Ile-207 and Phe-352 residues of the target protein.

The activity of the most active compound **12** can be attributed to strong hydrogen bond formation of 1.941 Å between the hydrogen of secondary amine and hydroxyl oxygen of Tyr-444. The hydrogen atom of the O—H group in Tyr-444 is attached to the oxygen by a covalent bond and the lone pair of electrons at oxygen (of O—H in Tyr-444) is still available to form a hydrogen bond with the hydrogen atom of secondary amine of **12**. Here, Tyr-444 acts as the hydrogen bond acceptor, while **12** acts as the hydrogen bond donor. As we know, hydrogen bonding takes place between the most electronegative atom and the comparatively electropositive hydrogen atom. The nitrogen atom of secondary amine is less electronegative due the amide-delocalization. We consider it as an amide, because the C=O functionality is adjacent to it. In this case, the oxygen atom of C=O in oxindole moiety of **12** is the better hydrogen bond acceptor but polar hydrogens are present nowhere nearby up to a distances of 2.5–2.6 Å. Therefore, the only possibility of hydrogen bond formation remained was with the polar hydroxyl oxygen of Tyr-444. Based on these observations, we can conclude that hydrogen bond formation between the secondary amine of **12** and the Tyr-444 of MAO-A was quite obvious and was responsible for the activity of the lead compound **12**.

**Table 3**
In vitro MAO-A inhibition assay results

| Compound | MAO-A inhibition activity ($IC_{50}$ μmol ± SEM) |
|---|---|
| **9** | 29.5 ± 0.68 |
| **11** | 27.2 ± 1.12 |
| **12** | 18.27 ± 0.81 |
| **19** | 35.1 ± 1.88 |
| Moclobemide | 13.1 ± 0.96 |
| Clorgyline | 3.65* ± 0.27 |

* Activity in nmol.

**Table 4**
Estimated free energy of binding of synthesized compounds in the target MAO-A

| Compound | Estimated free energy of binding (kcal/mol) |
|---|---|
| **3** | −4.27 |
| **4** | −4.05 |
| **5** | −4.03 |
| **6** | −4.14 |
| **7** | −4.39 |
| **8** | −4.44 |
| **9** | −4.88 |
| **10** | −4.31 |
| **11** | −4.87 |
| **12** | −4.95 |
| **13** | −3.68 |
| **14** | −3.90 |
| **15** | −3.69 |
| **16** | −4.62 |
| **17** | −4.29 |
| **18** | −4.17 |
| **19** | −4.66 |
| **20** | −4.41 |

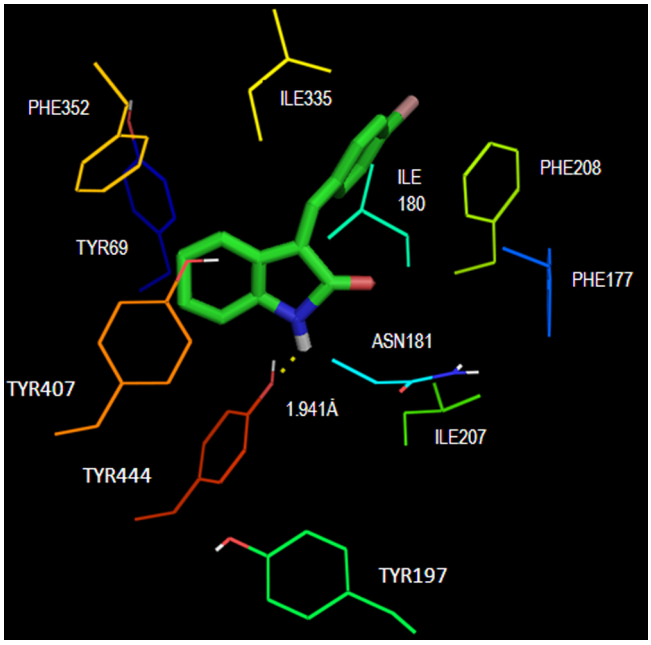



**Figure 5.** Docking of compound **12** in the active site of human MAO-A. The amino acids involved in the hydrogen, hydrophobic, and van der Waals interactions with **12**, are highlighted.

In conclusion, a series of 3-substituted oxindole derivatives were designed and synthesized in search of potent antidepressants. The pharmacological results revealed that synthesized compounds showed significant activity and compound **12** was found to be the most active with a potency comparable to that of the imipramine in the in vivo models and similar to the moclobemide in the in vitro MAO-A inhibition assay. The preliminary structure-activity relationship (SAR) study revealed that the substitution of bromo atom on phenyl, furanyl, and thienyl rings was critical for the activity and imparted superior activity when bromo atom was placed at the 4-position of the phenyl (**12**), 3-position of the phenyl (**11**), and 5-positions of the furanyl (**16**), and thienyl rings (**19**). Additionally, the electronegative nature of the halogen substituents also affected the activity. It was found that the compounds possessing the least electronegative halogen atom (bromine atom) were reasonably more active than the compounds bearing atoms of higher electronegativity, such as chloro and fluoro atoms at the analogous positions. Although, when the chlorine

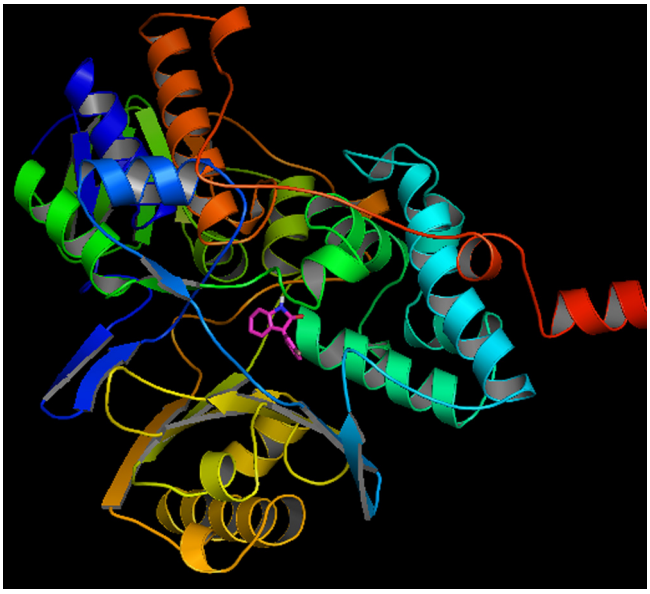


**Figure 6.** Stereoview of the docked structure of compound **12** into the active site of human MAO-A.

atom was present at the 4-position of the phenyl ring in compound **9**, it still retained the activity, indicating the importance of substituent at the *p*-position. The compounds with nitro and alkyl substituents were moderately or less active. Taken together, our results have opened a new window in the field of behavioral pharmacology of chalcones. Additional studies are needed to further optimize the pharmacophore to augment the central effects of the chalcones.

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## Supplementary data

Supplementary data ($^1$H NMR spectra of all the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.09.048.

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