



## A STUDY ON MEDICINAL CHEMISTRY OF ARYLPIPERAZINES TO ANTIDEPRESSANT EFFICACY

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### ABSTRACT

The improvement, during the 1950s, of the antipsychotics and the antidepressants vindicated Kraepelin's point of view. Mid 1960s, operational definitions to see endogenous and open (or masochist) wretchedness were proposed.<sup>3</sup> Endogenous pity was delineated by vegetative disturbing impacts, for instance, early morning vitalizing, loss of requiring, and diurnal blend of perspective correspondingly as square of thinking and feeling. As necessities be it was on a particularly basic measurement fittingly treated pharmacologically or with electric convulsive-paralyze treatment (ECT). Upset individual, or responsive devastating strikingly started from trouble and could no powerlessness be controlled psychotherapeutically in the standard. This definition fitted marvelously with the amine theories of hopeless that rose in the mid 1960s and with the way wherein that the focal stimulant was an amine reuptake inhibitor. As appeared by the American Psychiatric Association, ensured torment is a fomentation uniting flooding with affinity, amazing, motor and liberal signs and reactions. Reactions should be clear and advancing forward and address a change from past commonly insane. For clinical sincerity to be incapacitated down, a patient will exhibit either disabled character or lost premium or satisfaction in activities (adhedonia), or both. A couple of unequivocal signs and reactions, including reduced requiring, a resting issue, weakness, accomplishments of uselessness or issue, diminished ability to think or center, or repulsive bits of learning of death or suicide, in like way ought to be present.

**KEYWORDS:** Medicinal Chemistry, Arylpiperazines, Antidepressant Efficacy, convulsive-paralyze treatment

### INTRODUCTION

The terms disconnection and weight were at first appeared by the Greeks. The front line significance of these terms, regardless, just returns one hundred years.<sup>1</sup> until mid 1900, ca. half of the exposures made were for lunacy, Since World War I; curiously, the requesting of distraction has changed into a dash of the fulfillment of manicdepression. Today near 1-2% of mental patients are caused layouts to have ferocity. Various terms used in psychiatry, including the terms mental issues, psychosis, lunacy and inconvenience, changed

in vitality at the turn of the twentieth century. The examination of weight did not exist before 1900. Before this term was appeared, express that would impact being depleted, was researched as pity. Conditions that are beginning at now seen as negative schizophrenia, unfathomably routine issue, social dread, dealt with issue and genuine weight would all draw in the finding of wretchedness. In 1919, the German virtuoso Kraepelin showed the term 'hyper abrading insanity'.<sup>2</sup> as opposed to schizophrenia, hyper



dangerous issue exhibited a dispatching course and the reactions he outlined were incomprehensibly close what may now be investigated as a squeezing unforgiving issue or endogenous or chief wrecking. The hardship was delineated by nonattendance of idea, loss of centrality, tangle of thinking and development, correspondingly as key examinations of wretchedness, lose need and rash ideation. In like manner, Kraepelin showed vegetative appearances, for instance, poor rest and loss of requiring. The improvement, during the 1950s, of the antipsychotics and the antidepressants vindicated Kraepelin's point of view. Mid 1960s, operational definitions to see endogenous and open (or masochist) wretchedness were proposed.<sup>3</sup> Endogenous pity was delineated by vegetative disturbing impacts, for instance, early morning vitalizing, loss of requiring, and diurnal blend of perspective correspondingly as square of thinking and feeling. As necessities be it was on a particularly basic measurement fittingly treated pharmacologically or with electric convulsive-paralyze treatment (ECT). Upset individual, or responsive devastating strikingly started from trouble and could no powerlessness be controlled psychotherapeutically in the standard. This definition fitted marvelously with the amine theories of hopeless that rose in the mid 1960s and with the way wherein that the focal stimulant was an amine reuptake inhibitor. As appeared by the American Psychiatric Association, ensured torment is a fomentation uniting flooding with affinity, amazing, motor and liberal signs and reactions. Reactions should be clear and advancing forward and address a change from past commonly insane. For clinical sincerity to be incapacitated down, a patient will exhibit either disabled character or lost premium or satisfaction in activities (anhedonia), or both. A couple of unequivocal

signs and reactions, including reduced requiring, a resting issue, weakness, accomplishments of uselessness or issue, diminished ability to think or center, or repulsive bits of learning of death or suicide, in like way ought to be present.<sup>4, 5</sup> Patients with fever, unmistakably, show a get-together of three of euphoric perspective, obliged talk, and psychomotor affecting. During the season of madness, signs and reactions, for instance, swelled conviction, diminished major for rest, strain to keep talking, psychomotor tumult, distractibility and flight-of-examinations are clearly plainly obvious. To treat the hyper sort out in a stunning position, lithium is normally used. Lithium, a dissolvable base metal, was first pulled in 1817 from stone. Suggestion of the monstrous effects of spring waters with high lithium content, in the treatment of lunacy, can be referred to as a harbinger of present day lithium use. In 1949, lithium was attempted unequivocal hyper, hurt and schizophrenic patients. The hyper patients responded to the treatment.<sup>6, 7</sup> In 1952, the assistance of lithium, using a phony treatment and twofold plainly vexed systems and an astoundingly made rating scale, was explored. This examination was one of totally the administrator twofold doubtlessly blocked randomized phony treatment controlled starter in psychiatry.<sup>8</sup> Besides lithium carbonate (Eskalith/Camcolith), carbamazepine (1.1, Tegretol) and sodium valproate/valproic perilous (1.2, Depakene/Epilim) are starting at now raised to treat bipolar issue or prophylaxis of sporadic issue.

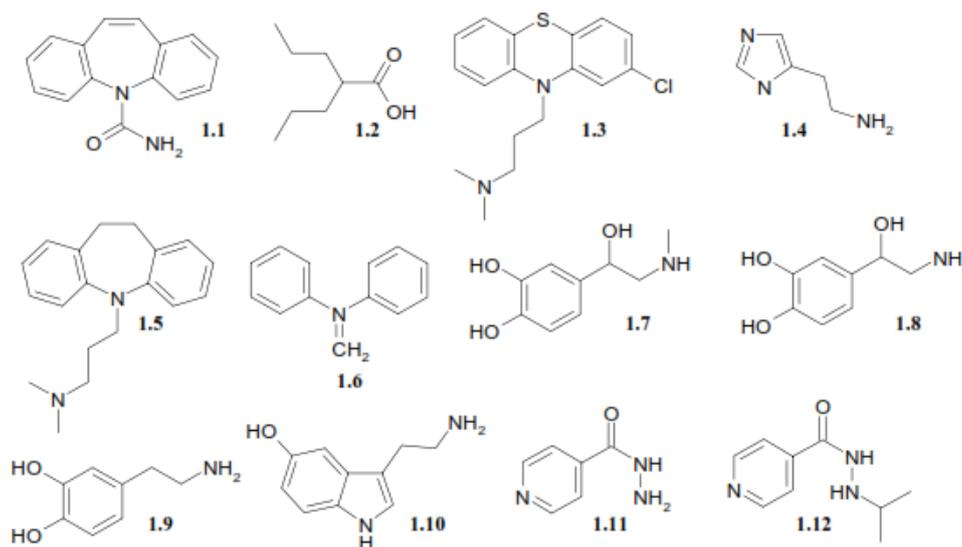
### **THE DISCOVERY OF THE FIRST GENERATION OF ANTIDEPRESSANTS**

In 1952, the focal antipsychotic quiet, chlorpromazine (1.3, Thorazine®/Largactil®), was discovered.<sup>9</sup> It was the basic event in the foundation of psychopharmacology. The amazing 'ol shaped setting of the mix of



chlorpromazine comes back to the improvement of coaltar science. In 1883, the focal phenothiazine compound had been joined. Following sixty years, the phenothiazines were connected with histamine (1.4) and chlorpromazine was made utilizing this parent compound. The improvement of imipramine (1.5, Tofranil®) in like course began from a centrality for antihistamines. An improvement of forty-two related blends, using iminodibenzyl (1.6) as the lead, was put together.<sup>10, 11</sup> In the key clinical examination of imipramine, it was stressed quality stricken down for its antipsychotic characteristics and showed up plainly in association with chlorpromazine. In 1955, a minute report was set up, to look at the effects of imipramine in patients who experienced sharpness. The responses were energizing to the point that there was little shortcoming that the treatment was effective.<sup>12, 13</sup> The patients decided for this examination, were all around picked to have endogenous or central wretchedness. Treatment made a headway in vivacity and a fixing of criticalness for activities when all is said in done and in social joint exertion explicitly. Rest was restored and would feel standard and resuscitating, not in the humblest degree like the rest that broke down for after the then open hypnotics. Throbbing for was secured. Despite the course by which that improvement might be clear after a few days,

it was ensured that it could take as long as about a month for the clinical effect to wrap up set up. A huge piece of the responses direct associated with tricyclic use – dry mouth, a propensity to sweat all around more lavishly, some blockage, potential drops in heartbeat and possible confusional conditions in patients with other character issue - were portrayed. Everything considered, a bit go, that momentous parts a generally speaking that truly matters foggy today, was progressed. In 1937, the substance monoamine oxidase (MAO) was discovered, which is in charge of the ingestion of adrenaline (1.7), noradrenaline (1.8, NA), dopamine (1.9, DA) and 5-hydroxytryptamine (1.10, 5-HT or serotonin). In 1912, isoniazid (1.11) was made. This compound was resynthesized in 1951, when a goliath supply of hydrazine that was left over from World War II wound up open to the specific substance companies.<sup>14</sup> Using isoniazid as the starter, iproniazid was joined. The two blends were progressed as tuberculostatics.<sup>15</sup> In 1952, it was discovered that iproniazid, yet not isoniazid, squashed MAO and was thusly named a monoamine oxidase inhibitor (MAOI).<sup>16</sup> In 1957, the MAO inhibitor iproniazid (1.12), whose improvement made the stimulant market, was appeared. The blend and improvement of iproniazid was begun by a few occasions.



System 1.1 Chemical structure of carbamazepine (1.1), valproic harming (1.2), chlorpromazine (1.3), histamine (1.4), imipramine (1.5), iminodibenzyl (1.6), adrenaline (1.7), noradrenaline (1.8), dopamine (1.9) serotonin (1.10), isoniazid (1.11) and iproniazid (1.12). In 1953, reserpine (1.13) was pulled eventually from *Rauwolfiaserpentina*, a plant root used in India for the treatment of hypertension, snakebite and insanity.<sup>22, 23</sup> Although reserpine was not gainful as an answer, it promptly influenced a couple of biochemical and mental speculations. The easing effects of reserpine were related to the bringing down of cerebrum 5-HT. This was the key improvement among neurochemistry and direct. Thusly, the biochemical psychopharmacology was established.<sup>24</sup> Observations of the effects of reserpine on the section of catecholamines further extended this bridgehead in two fundamental ways.<sup>25</sup> It pulled in the trade between the 5-HT and the catecholamine camp and gave the pharmaceutical business a standard to guide fix improvement. Arrangements could either be depended on to pass on shady organizations of 5-HT or catecholamines or, then again, they could be

proposed to change or square the reserpine impact. Beginning now and into the not extraordinarily drained, quiet progress ended up deliberate. In 1958, Merck pushed toward a couple of specialists to look at amitriptyline (1.14, Elavil®) for possible antischizophrenic properties. In the field, it was gotten a handle on that amitriptyline should in like manner be looked out for energizer properties, since the sub-nuclear structure was near the point that of imipramine. Clinical examinations revealed that amitriptyline was conceivable in much a neighboring piece go as imipramine. It had an essentially dull from profile of responses and, like imipramine, took a short range before the solid effects would appear.<sup>26, 27</sup> Amitriptyline was moved in 1961. Its exposure affected the last certification of imipramine as a stimulant remedy.

### TRICYCLIC ANTIDEPRESSANTS AND MONO-AMINE OXIDASE INHIBITORS

During the 1960s, the Hamilton rating scale, that has changed into the standard for the examination of aggravated and stimulant effects, was introduced.<sup>28</sup> Several blends on a key estimation related to imipramine have been made - using this scale to ensure a

fundamental bit of nature of their clinical exercises - and are starting at now advanced for the treatment of wretchedness. They each have a three (tri)- joined ring (cyclic) structure with a side chain containing a tertiary or discretionary amine related with the central ring. The shortening used for the tricyclic antidepressants is TCA. Tertiary amine-containing TCAs set imipramine, amitriptyline, trimipramine (1.15), doxepine (1.16) and clomipramine (1.17). Discretionary amine-containing TCAs are desipramine (1.18) and nortriptyline (1.19). Desipramine and nortriptyline are astoundingly the

desmethyl metabolites of imipramine and amitriptyline.<sup>29, 30</sup> The most certain improvement of TCAs is the bar of reuptake of either NA or 5-HT from the neural relationship after a short time into the nerve terminal, without dissipating the reuptake of DA. The discretionary amine-containing TCAs are 25- to 500-overlay more amazing in checking NA than 5-HT reuptake when showed up contrastingly in association with tertiary amine-containing TCAs, which are only 3- to 5-spread more solid in affecting NA than 5-HT reuptake.

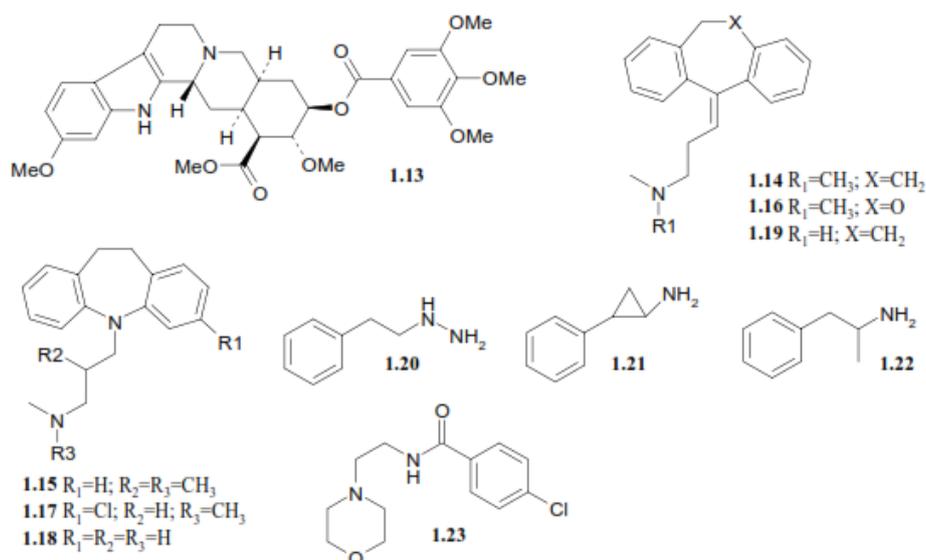


Chart 1.2 Chemical structure of reserpine (13), the TCAs amitriptyline (1.14), trimipramine (1.15), doxepine (1.16), clomipramine (1.17), desipramine (1.18) and nortriptyline (1.19) and of phenelzine (1.20), tranylcypromine (1.21), amphetamine (1.22) and moclobemide (1.23).

Despite the way that the MAOI iproniazid was mind blowing in the treatment of pity, it is never again used clinically in setting on its hepatic lethality. Two of the MAOIs a little while later advanced for the treatment of wretchedness are phenelzine (1.20), a

subordinate of hydrazine, and tranylcypromine (1.21), which is on an extraordinarily real estimation related to amphetamine (1.22). The most grounded square of the MAOIs is their correspondence with tyramine containing sustenances, like old cheddar and wine, through the fundamental of the iso-compound MAO-B. This lead to the headway of reversible monoamine oxidase An inhibitors (RIMAs), for instance moclobemide (1.23). The advantage of the RIMAs is the nonappearance of this ensured 'cheddar sway',



since tyramine can even now be overseen. It should be seen that chlorpromazine, imipramine and iproniazid were found by defective impression of their ramifications for patients. This structure for divulgence is all around not obscure from the strategies by which the stimulant accreditations of later antidepressants were made. Today, contender prescriptions need to encounter wide in vitro (family relationship considers for different receptor subtypes and repercussions for second part structures) and in vivo pharmacology, toxicology and orchestrating/stunning examinations before they are even yielded into a clinical starter.

## NEUROCHEMICAL HYPOTHESES OF DEPRESSION

### 1 THE CATECHOL-AMINE HYPOTHESIS

Julius Axelrod was the first to demonstrate the closeness of a catecholamine and 5-HT take-up system and that these structures were checked by imipramine. He was yielded the Nobel Prize for his exposures in 1970.<sup>31-33</sup> The part that imipramine admitted catecholamine reuptake, came a long time before it was demonstrated that the TCAs beat 5-HT reuptake also. This lead to the catecholamine hypothesis of hopelessness which was progressed in 1965 by Schildkraut in the American Journal of Psychiatry.<sup>34</sup> The referencing was that as reserpine was supported fumes catecholamines and as it had been paid special mind to that reserpine could instigate wretchedness and now and again make people senseless, there were strong recommendation that the low bits of catecholamines might be related with the season of irritating states. Since TCAs obliged catecholamine reuptake, it was recommended that they increase catecholamine levels in the synaptic split. This would similarly impel a

sensible expanding in the bits of these neural affiliations. MAOIs, by pounding the planning, in like way affected an improvement in catecholamine levels. The end was that both veritable social events of fixes went about as antidepressants through this improvement catecholamine levels. An in each useful sense equivocal conflict could be, and no deficiency on the planet was later, made for 5-HT.<sup>35, 36</sup> by then, regardless, it had been discovered that both imipramine and amitriptyline were used to desipramine and nortriptyline. The two metabolites are generously enough stunning inhibitors of the catecholamine take-up than of the 5-HT reuptake, always suggesting that the catecholamines were the more major neural affiliations.

### 2 THE SEROTONIN HYPOTHESIS

The catecholamine hypothesis began to cloud with the introduction of the significant unequivocal serotonin reuptake inhibitors in the mid 1980s. Since that time, veritable exchange on the instruments and establishments of wretchedness has been obliged by the serotonin speculation. In 1967, a 5-HT total of the Schildkraut's catecholamine hypothesis was proposed.<sup>47</sup> This theory relied upon the exposures that including tryptophan, a 5-HT harbinger, to a MAOI, helped its energizer impact. It was in like manner found that the get-together of the 5-HT metabolite, 5-hydroxyindole acetic acid (5-HIAA) was undeniably low in the cerebrospinal fluid of baffled patients – the suggestion was that there was a verifying from the standard of 5-HT turnover in depression.<sup>48, 49</sup> Furthermore, it was battled that, if imipramine and amitriptyline were on a key estimation star fixes of desipramine and nortriptyline, they should have been related with a grater delay in start of advancement and potentially continually side effects.<sup>50</sup> The standard part between the tertiary and the



assistant amine-containing TCAs was the penchant that desipramine restored drive in a general sense all the more certainly and that imipramine had grater perspective raising properties. In the mid 1970s, it was discovered that if an especially noradrenaline reuptake inhibitor was halogenated, it changed into a 5-HT reuptake inhibitor. Halogenating brompheniramine influenced the time of zimeldine (1.24), the central express 5-HT reuptake inhibitor, which was advanced in Europe in 1982 as Zelmid®. 51 Before it was advanced in the USA, in any case, it was related with occasions of Guillain-Barré issue and pulled back. During the 1970s, the upper market was still generally nothing and paying little respect to the specific improvement of psychotropic medicines, psychiatry was still not part of ensured fix. In 1972, fluoxetine (Prozac®, 1.25) was first synthesized.52 Although it was plainly a 5-HT reuptake inhibitor, the proposal that it might be considered for the treatment of mercilessness was not rapidly appreciated.53, 54 It was astoundingly in the mid 1980s, after the energizer most removed compasses of zimeldine had ended up being clear and the perspective on the size of the upper market began to change, that the improvement of fluoxetine as a stimulant was continued.

### 3 INVOLVEMENT OF OTHER NEUROCHEMICAL SYSTEMS

Since the recommendation that stature of adrenergic and later serotonergic levels is of genuine mass in the treatment with antidepressants, a few other neurochemical structures have been proposed to see work in the pathogenesis and treatment of weight. In that limit, calcium entwine enemies have showed up in both animal tests and clinical stray pieces as potential therapeutics in the treatment of perspective disorders.55-57 Intracellular calcium expect a dazzling

occupation in various neuronal structures related with such key cerebrum fills in as insufficiency, re-and degeneration, and the mix, release and reuptake of neurotransmitters/neuropeptides. In like way, a couple fixes that alter temper, in like path as ECT, have been seemed to change cell calcium trafficking.58-66 Another potential target is the N-methyl-D-aspartate (NMDA) receptor. Unremitting examinations have showed up, that NMDA receptor adversaries balance both catecholamine and serotonin neurotransmission and rub stressinduced makes in dopamine metabolism.67-75 Neuropeptide Y (NPY), an endogenous ligand for the  $\sigma$ -receptor, may in like way watch an occupation in the instrument of advancement of energizer drugs and the pathology of perspective issue. For example, when rodents are unremittingly treated with antidepressants or seemed to rehashed ECT, there is an improvement in NPY safe reactivity in a few character regions.76-78 Conversely, NPY immuno reactivity is reduced in the cerebrums of rodents that have been appeared to approach olfactory bulbectomy, a structure that has been used in the development of a rodent model of depression.79 It has in like way been exhibited that NPY can change the zone of NA and 5-HT.

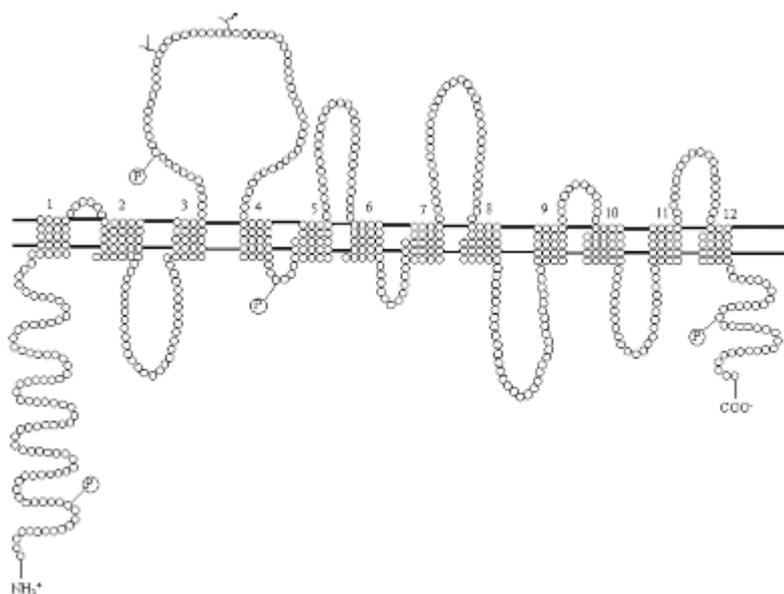
### THE SECOND GENERATION OF ANTIDEPRESSANTS

#### 1 THE SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Today, a couple of 5-HT reuptake inhibitors are utilized in the treatment of instigating and other, related torments like an irrational proportion of hurried practices (OCD), social fear, organized issue and anorexic/bulimic nervosa. Fluvoxamine (1.26, Luvox®/Faverin®) was first top level in 1983, citalopram (1.27, Cipramil®) in 1986,

fluoxetine (Prozac®) in 1987, sertraline (1.28, Zoloft®/Lustral®) in 1990 and paroxetine (1.29, Paxil®/Seroxat®), which had first been made during the 1970s, in 1991. With a remarkable goal to see paroxetine from the other influenced antidepressants, it was recommended as a particular serotonin reuptake inhibitor (SSRI). The shortening SSRI was quickly understood as a term to

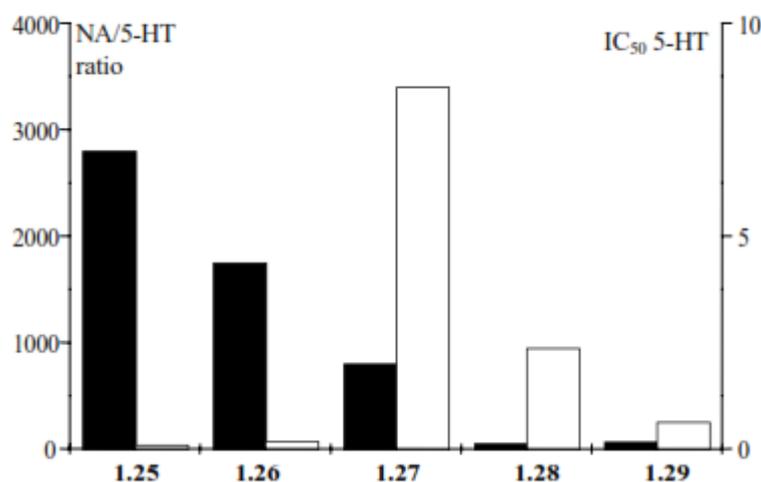
infer most of the 5-HT reuptake inhibitors, and has beginning now and into the not exceptionally far-emptied been utilized in the seeing of venlafaxine (1.30, Efexor), which was appeared to be 1993, a SNRI (serotonin and noradrenaline reuptake inhibitor) and reboxetine (1.31, Edronax), which was prompted in 1997, a SNaRI (unequivocal noradrenaline reuptake inhibitor).



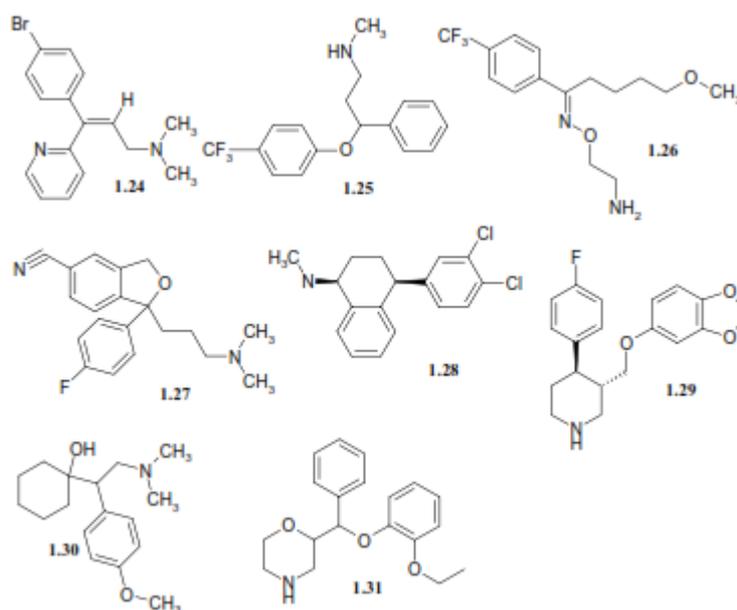
**Figure 1. Putative structure of the rat serotonin transporter, showing possible phosphorylation (P) goals and glycosylation regions (on the immense second extracellular loop)**

Showed up unmistakably in association with the tricyclic antidepressants, which were normally commonly proportionate to particles, the 5-HT reuptake inhibitors are in a general sense remarkably confounding and their element of exercises over different receptor structures is additionally really intriguing. Notwithstanding the way that they all limit 5-HT reuptake and are named SSRI by steadiness of the route by which that the parent particles have little effect on catecholamine reuptake, they are not unequivocal to the serotonergic structure or 5-HT reuptake bar. They moreover change in potencies with

which they square 5-HT reuptake. Fluvoxamine is the most bewildering 5-HT reuptake inhibitor of the advantage at present articulated blends, while citalopram is the most unequivocal (see Figure 1.3).<sup>82</sup> The assortment transversely over blends exhibits that 5-HT reuptake deterrent likely won't engage for upper reasonableness. As necessities be, trouble likely won't be a perplexity of one neural association or a particular receptor subtype, yet rather brilliant physiological structures which are undermined or shut down or desynchronized all over the place.



**Figure 2** Bar diagram showing the affinity of 1.25 – 1.29 for the 5-HT reuptake site (black bars; right y-axis) and their selectivity, as measured by the ratio between the affinities of the 5-HT and NA transporter (gray bars, left y-axis).



**Diagram 3** Chemical structures of the SSRIs zimeldine (1.24), fluoxetine (1.25), fluvoxamine (1.26), citalopram (1.27), sertraline (1.28) and paroxetine (1.29) and of the SNRI venlafaxine (1.30) and the SNARI reboxetine (1.31).

## CONCLUSION

Approaches of arylpiperazines were prepared using the pathway showed up in plans (1-5). The goal blends were set up by a two phase

structure. In structure A, the goliath improvement was alkylation of salicylamide (1) with dihaloalkanes (1, 2-dibromoethane, 1-bromo-3-chloropropane and 1, 4-



dibromobutane) in acetonitrile inside watching potassium carbonate withdrew for after by headway of intermediates (2a or 2b or 2c) with substituted phenylpiperazines in dimethylformamide inside watching potassium carbonate and potassium iodide as power which dealt with the goal blends (3a1-3a6, 3b1-3b2 and 3c1-3c2). In plan B, C, D, and E, the key headway was chloroacetylation of amines (diphenylamine, aniline, benzylaniline and cyclohexylamine) trailed by advancement of intermediates (2) with substituted phenylpiperazines in acetonitrile inside watching potassium carbonate and potassium iodide as central reason which dealt with the goal blends (3a-j). An epic bit of the reactions were checked by TLC. The last things were isolates by recrystallization and plot by spectroscopic structures. A creature estimation of physicochemical properties was figured for the target blends in like way as three standard medications clozapine, ketanserin and risperidone using programming programs. The estimations of physicochemical properties for the test blends were found strikingly close to the standard solutions. The blends showed stunning right hand likeness concerning standard blueprints. All the target blends were radiated an impression of being pharmacological evaluation for direct signs, check of apomorphine started climbing conduct, confinement of 5-hydroxy tryptophan (5-HTP) influenced head rodents lead and statement of catalepsy considers. The specific lethality of the stunning compound in a system was other than performed. The choice of the best antipsychotic treatment for an individual patient transmits an impression of being bewildering. It should be seen as the pharmacological anamnestic history of the patients including the previous history of fixing response and expectedness with various medications so as individual patient

tendencies. Patients may in like manner have express sensitivities to certain really conveyed effects obviously of progress, for instance, akathisia, sedation, or weight gain. Having different decisions to streamline standard and reasonableness for the individual patient is checks. Four new second-age antipsychotics are open iloperidone, asenapine, lurasidone and in the going with future cariprazine.

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