A Practical Synthesis of 5-Aroyl-1-aryltetrazoles Using an Ugi-Like 4-Component Reaction Followed by a Biomimetic Transamination

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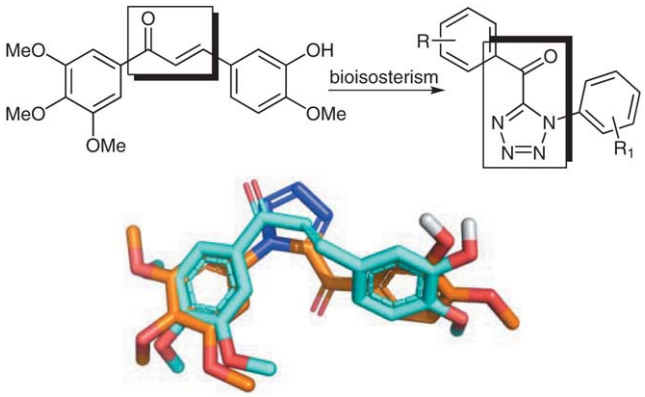
Abstract: Multicomponent reactions (MCRs), followed by subsequent transformations, are fascinating tools for the rapid and effective synthesis of molecular scaffolds with potential pharmacological relevance. We became interested in the preparation of novel 5-aroyl-1-aryltetrazoles as (1) they still represent challenging structures not easily accessible through the methods described in literature, and (2) the α-ketotetrazolic framework may be considered as a potential bioisostere of the enonic linker of chalcones. In the present work, a novel, simple, effective and general synthesis for this class of compounds is described.

Key words: 5-aroyl-1-aryltetrazoles, multicomponent reactions, isocyanides, Ugi reaction, chalcones

Multicomponent reactions (MCRs) are one-pot processes that combine at least three substrates to deliver a single complex product, incorporating essentially all of the atoms of the starting materials.[1] Usually, MCRs are flexible, convergent, and atom-efficient processes with a high exploratory power.[2] This sort of 'ideal synthesis'[3] is experiencing a growing interest, also due to the possibility of incrementing the complexity and diversity of the molecular scaffolds by employing substrates able to undergo secondary transformations.[4] In this way, large libraries of complex substances, not easily accessible through conventional two-component multistep synthesis, can be quickly accessed speeding up the drug discovery process.

Post-transformation reactions are countless, starting from classic textbooks organic reactions such as Pictet–Spengler cyclization,[5] intramolecular Diels–Alder reaction,[6] Mitsunobu reaction and acyl migration,[7] Knovenagel condensation,[8] amide reduction,[9] metathesis reaction[10] – just to cite few of them – to sequential multi-component transformations such as Ugi–Ugi[11] and Ugi–Petasis.[12]

Herein, we describe a novel and operationally simple strategy for the synthesis of elusive 5-aroyl-1-aryltetrazoles by means of an Ugi-like four component reaction (4-CR), followed by a hydrogenolysis/transamination post-transformation. Our interest in 5-aroyl-1-aryltetrazoles arose from the possibility of using this molecular scaffold as a replacement of chalcones,[13] in order to generate metabolically stable chalcone-like analogues with antitubulinic activity (Scheme 1).[14]



Scheme 1 Superimposition between a potent antitubulinic chalcone and 5-aroyl-1-aryltetrazoles

Surprisingly, SciFinder® and CrossFire® surveys revealed that only four 5-aroyl-1-aryltetrazoles have been reported to date. This paucity has to be ascribed to the poor chemoselective and low yield synthetic routes developed so far. Indeed, only two synthetic strategies have been reported (Scheme 2).

In the first strategy, nitrones react with hydrazoic acid followed by an intramolecular [1,3] cycloaddition,[15] while the second synthetic strategy consists in the reaction between isocyanides and acyl chlorides to give α-ketoimidoyl chlorides, which undergo nucleophilic substitution with an excess of hydrazoic acid, followed by an intramolecular [1,3] cycloaddition.[16] Very recently, the Sharpless group has devised a synthesis of 5-acyltetrazoles from azides and acyl cyanides, but the reaction was incompatible with aryl azides in order to generate 5-aroyl-1-aryltetrazoles.[17]

In a first attempt, the possibility to synthesize this scaffold was envisaged through a Passerini 3-CR using trimethylsilyl azide in the place of the acidic component, followed by an oxidation step (Scheme 3).

It is interesting to note that, in a comprehensive review on the Passerini reaction, there are no examples of tetrazole

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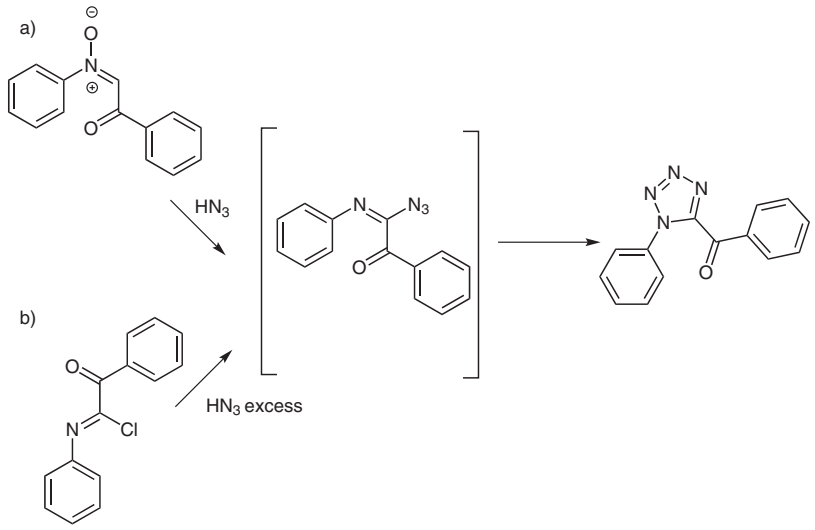
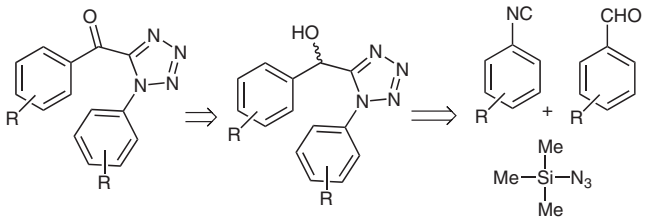


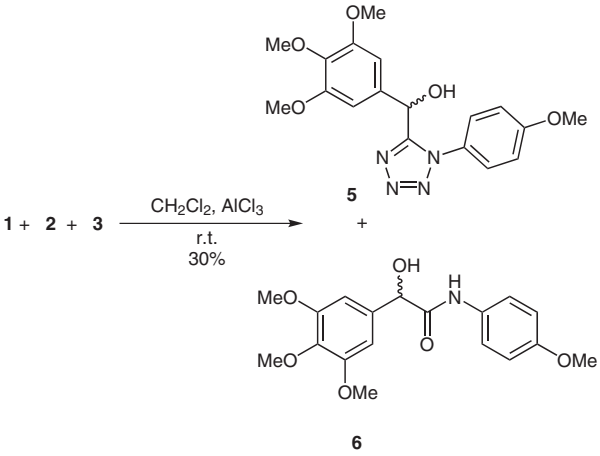
Scheme 2 Reported syntheses for the generation of 5-aroyl-1-aryltetrazoles



Scheme 3 First retrosynthetic analysis

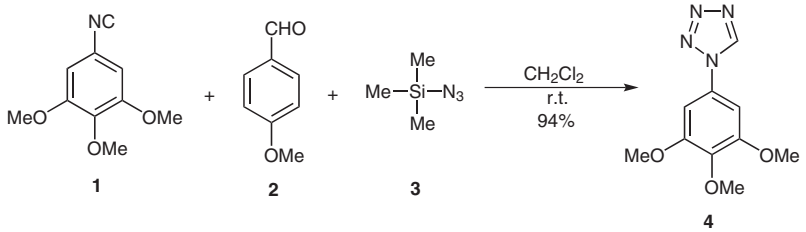
scaffolds generated by aromatic aldehydes and aromatic isocyanides.[18] When 3,4,5-trimethoxyphenyl isocyanide (**1**), *p*-anisaldehyde (**2**), and trimethylsilyl azide (**3**) were reacted in dichloromethane at room temperature, only the 3,4,5-trimethoxyphenyl-1*H*-tetrazole (**4**) was isolated in 90% yield (Scheme 4).[19]

Different Lewis acids as catalysts (zinc triflate, lithium bromide, indium trichloride, zinc chloride, aluminum trichloride, cerium trichloride, ytterbium triflate, boron trifluoride, and dysprosium acetate) were screened in order to activate the aldehyde component. The test reactions revealed that aluminum trichloride[20] was the only catalyst able to promote the multicomponent process, affording, after column chromatography, in 30% yield an inseparable mixture of the desired tetrazole compound **5** and the α-hydroxy amide product **6** in a 1:1 ratio (Scheme 5). The latter derives from water addition to the intermediate nitrilium ion. Attempts to avoid the formation of **6**, using anhydrous sodium sulfate, 4 Å molecular sieves, or ultra dry aluminum trichloride did not suppress the formation of the by-product **6**.[21] This strategy was therefore abandoned, as it suffered from low yields, formation of by-products, and difficult purification – features incompatible with the generation of a library during the drug discovery process.



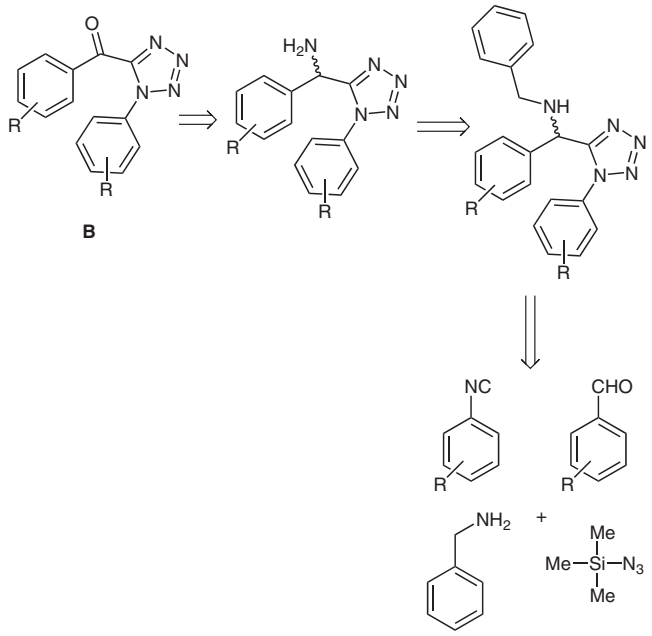
Scheme 5 MCR between an aromatic isocyanide, an aromatic aldehyde, and trimethylsilyl azide catalyzed by aluminum trichloride

Another retrosynthetic analysis was consequently devised, always using a MCR as key step for the introduction of all the functionalities in one single operation. In practice, the carbonyl group of 5-aroyl-1-aryltetrazoles could be created through a transamination reaction. The



Scheme 4 Formation of 3,4,5-trimethoxyphenyl-1*H*-tetrazole (**4**)

amine intermediate would derive from an Ugi-like 4CR using benzylamine, aryl isocyanide, aryl aldehyde, and trimethylsilyl azide[22] followed by a hydrogenolytic cleavage of the *N*-benzyl group (Scheme 6).



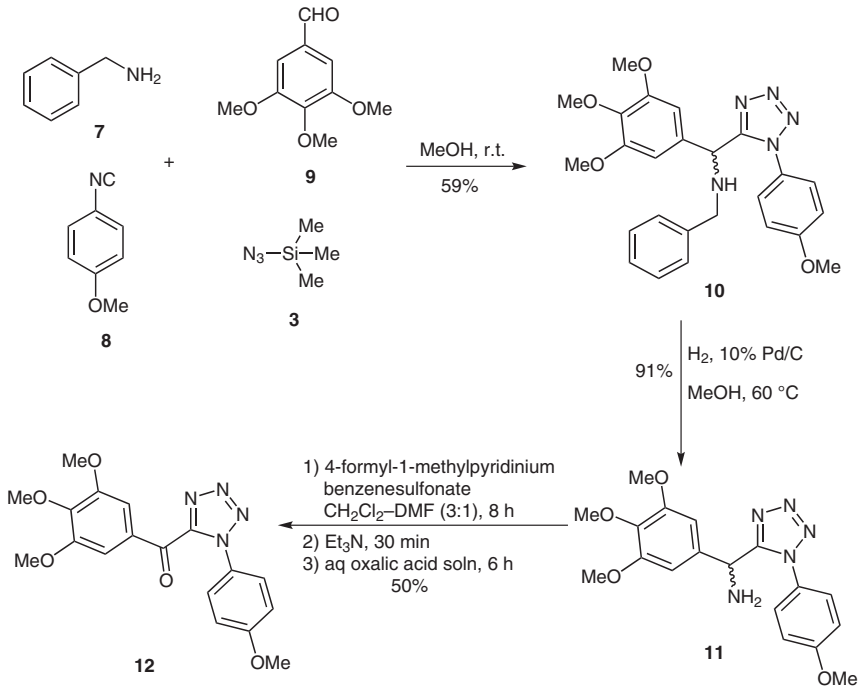
Scheme 6 Second retrosynthetic analysis

Initial experiments were carried out using benzylamine (**7**), trimethylsilyl azide (**3**), 4-methoxyphenyl isocyanide (**8**), and 3,4,5-trimethoxybenzaldehyde (**9**) as test substrates. The four compounds reacted in methanol at room temperature affording after 20 hours the desired adduct **10**, which precipitated and could be collected by simple filtration in 59% yield. Compound **10** was then hydrogenolyzed to cleave the benzyl group, using 10% palladium on charcoal as catalyst in methanol at 60 °C providing, after filtration over a Celite pad and evaporation of the solvent, the amino derivative **11** in 91% yield. Finally, **11** was subjected to the transamination reaction. After an extensive screening, we identified the Rapoport procedure[23] as the transamination reaction able to give the best yields, allowing us to isolate, after acidic workup and column chromatography, the 5-aroyl-1-aryltetrazoles derivative **12** in 50% yield (Scheme 7).

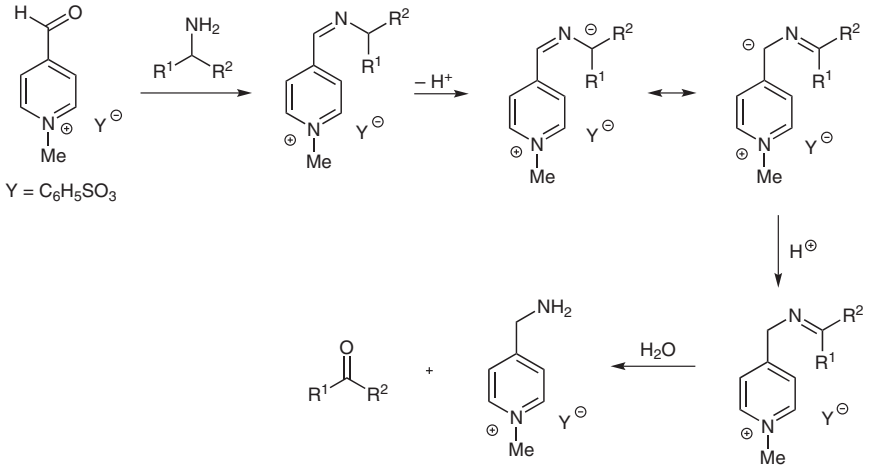
The Rapoport transamination reaction represents a simple and mild biomimetic conversion of amines to carbonyls in the presence of 4-formyl-1-methylpyridinium benzenesulfonate as pyridoxal phosphate (vitamin B_6) surrogate. The amine and the formyl derivative were stirred in CH_2Cl_2–DMF (3:1) for 8 hours at room temperature. Triethylamine was then added and deprotonation occurred under mild conditions forming an azaenolate. After about 30 minutes, the resonance-stabilized anion was protonated and hydrolyzed with an aqueous solution of oxalic acid to give the 4-(aminomethy)-1-methylpyridinium salt and the desired carbonyl compound (Scheme 8).

To demonstrate the scope and generality of this new synthetic strategy seven aldehydes **2**, **9**, **13**–**17** and seven isocyanides **1**, **8**, **18**–**22** with different electron-withdrawing and electron-donating substituents were employed (Figure 1).

Ugi-like 4-CR reaction was performed mixing the aldehyde, isocyanide, benzylamine, and trimethylsilyl azide in methanol (2 M) by stirring at room temperature for three days. All MCR products **10**, **23**–**35** were isolated in high yields (59–86%) (Figure 2).



Scheme 7 General procedure for the synthesis of 5-aroyl-1-aroyltetrazoles



Scheme 8 The Rapoport biomimetic transamination

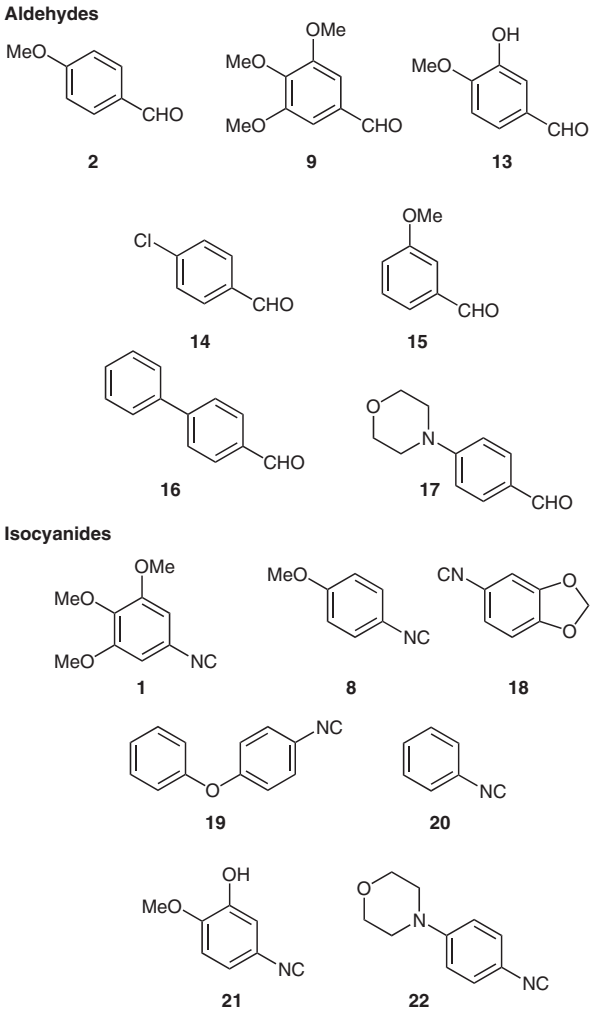


Figure 1 Structures of aldehyde and isocyanide building blocks

When the product was solid, it was isolated by just filtering the precipitate under vacuum, while, in the case of oily products, they were purified by chromatographic column using petroleum ether–EtOAc as eluent. Hydrogenolysis was carried out for 24 hours and the resulting primary amines **11**, **36–48** were isolated by simple filtration in excellent yields (60–95%) (Figure 3).

Finally, the amine derivatives were subjected to the biomimetic transformation giving the desired 5-aroyl-1-aryltetrazoles **12**, **49–61** in moderate to good yields (38–61%) (Figure 4).

In conclusion, we have reported a novel, efficient and versatile synthesis of 5-aroyl-1-aryltetrazoles, a class of molecules not easily synthesizable with the methods reported in literature. The use of a MCR followed by two post-transformation modifications allows the construction of this molecular scaffold in only three synthetic steps and the robustness of this methodology permits its use for the synthesis of libraries in the drug discovery programs. The biological evaluation of the synthesized products is underway and it will be reported in due course.

Commercially available reagents and solvents were used without further purification and were purchased from Fluka-Aldrich or Lancaster. Melting points were determined in open glass capillary with a Stuart scientific SMP3 apparatus and are uncorrected. All the compounds were checked by IR (FT-IR Thermo-Nicolet Avatar), ^{1}H and ^{13}C APT (Jeol ECP 300 MHz), and mass spectrometry (Thermo Finningan LCQ-deca XP-plus) equipped with an ESI source and an ion trap detector. Chemical shifts are reported in ppm. Column chromatography was performed on silica gel (Merck Kieselgel 70–230 mesh ASTM) using the indicated eluents. TLC was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm (Merck silica gel 60 F_{254}). When necessary they were developed with $KMnO_4$. Elemental analyses of all the 5-aroyl-1-aryltetrazoles (C, H, N) were within ± 0.4% of the calculated values, unless otherwise noted. Isocyanides **1**, **8**, **18–22** are described in literature. We synthesized them in two steps starting from the aromatic anilines, forming the formamide and dehydrating it with $POCl_3$. Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C.

CAUTION! Trimethylsilyl azide ($TMSN_3$) can release hydrazoic acid. Hydrazoic acid causes eye irritation, cough, headache, fall in blood pressure, weakness, palpitation, ataxia, and collapse. Certain tetrazoles are known to be explosive. In this lab, no problems have been encountered, but great caution should be exercised when heating compounds of this type. All experiments should be handled in an efficient fume hood behind a protection shield.

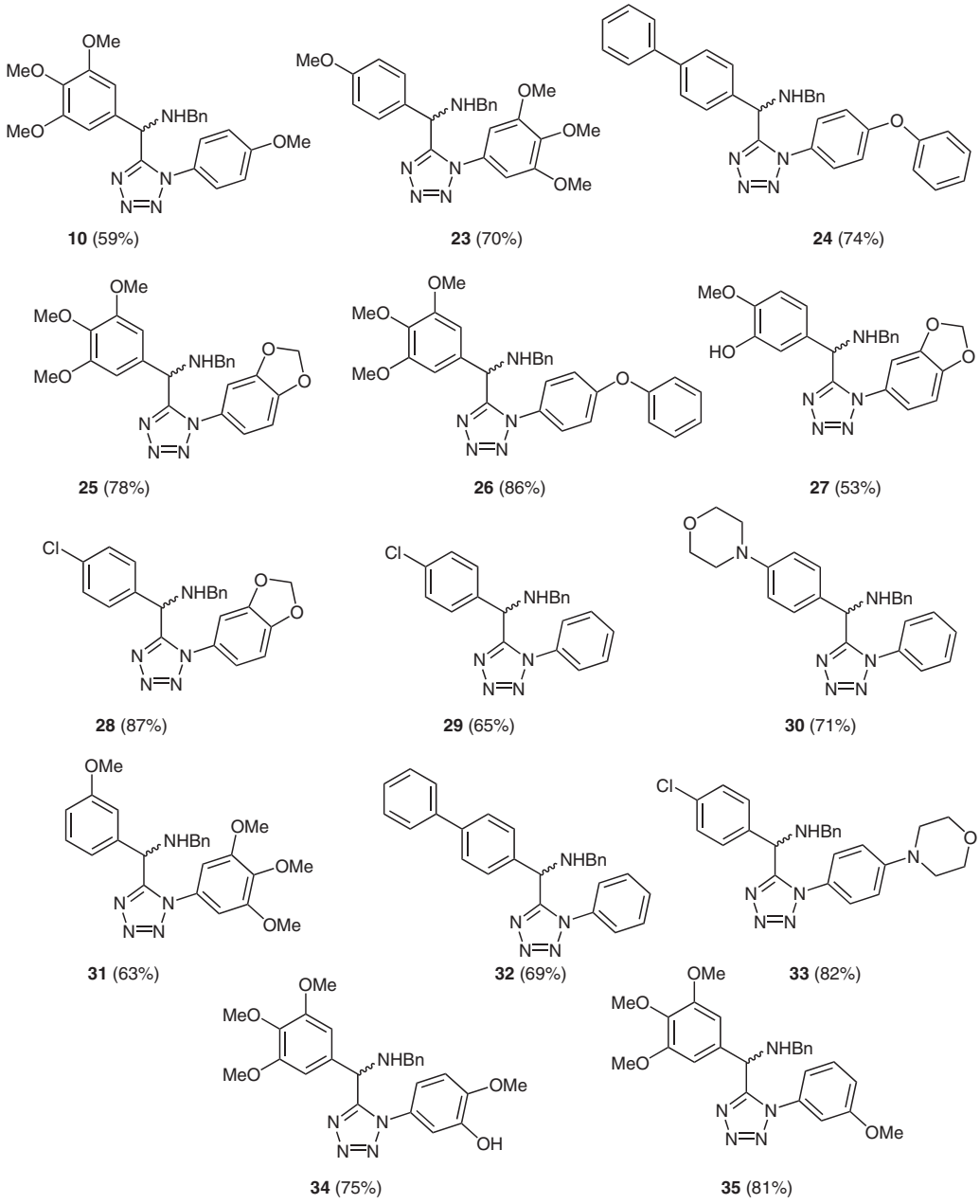


Figure 2 MCR products

5-Aroyl-1-aryltetrazoles; General Procedure

Aromatic isocyanide (20 mmol), aromatic aldehyde (20 mmol), *N*-benzylamine (20 mmol), and trimethylsilyl azide (20 mmol) were dissolved in anhyd MeOH (40 mL, 2 M) under N_2 atmosphere. The resulting solution was stirred at r.t. for 3 days. The solid formed was collected by filtration and washed with cold MeOH (10 mL). For oily products, the reaction mixture was evaporated and purified by column chromatography using PE–EtOAc as eluents. The obtained tetrazole intermediate was then stirred in MeOH (40 mL) under a H_2 atmosphere in the presence of 10% Pd/C by heating at 60 °C for 24 h. The crude reaction mixture was filtered through a Celite pad and evaporated to give the free amine pure enough for the following step. The amine was dissolved in CH_2Cl_2–DMF (3:1, 20 mL) and 4-formyl-1-methylpyridinium benzenesulfonate (1.2 equiv) was added. The reaction mixture was stirred at r.t. for 8 h, then treated with Et_3N (1.0 equiv) and stirred for 15–20 min. The reaction was finally quenched with cold sat. aq oxalic acid (25 mL) and stirred overnight. The mixture was then partitioned between H_2O (25 mL) and CH_2Cl_2 (50 mL). After extraction with CH_2Cl_2 (3 × 20 mL), the combined organic phases were washed with brine (1 × 25 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The carbonyl compound was purified by column chromatography using PE–EtOAc as eluent.

N-Benzyl-1-[1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl]-1-(3,4,5-trimethoxyphenyl)methanamine (10)

The crude material was filtered under vacuum and washed with cold MeOH to give a white solid (59%); mp 112–116 °C.

IR (KBr): 3290, 2943, 1591, 1323, 1256, 1131, 834 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.23 (m, 5 H), 7.01 (d, *J* = 8.2 Hz, 2 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 6.35 (s, 2 H), 4.88 (s, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.72 (s, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 160.4, 156.3, 155.5, 152.8, 137.9, 137.2, 127.8, 127.7, 126.7, 126.4, 125.3, 124.1, 113.9, 103.9, 60.1, 55.5, 55.41, 55.0, 50.5.

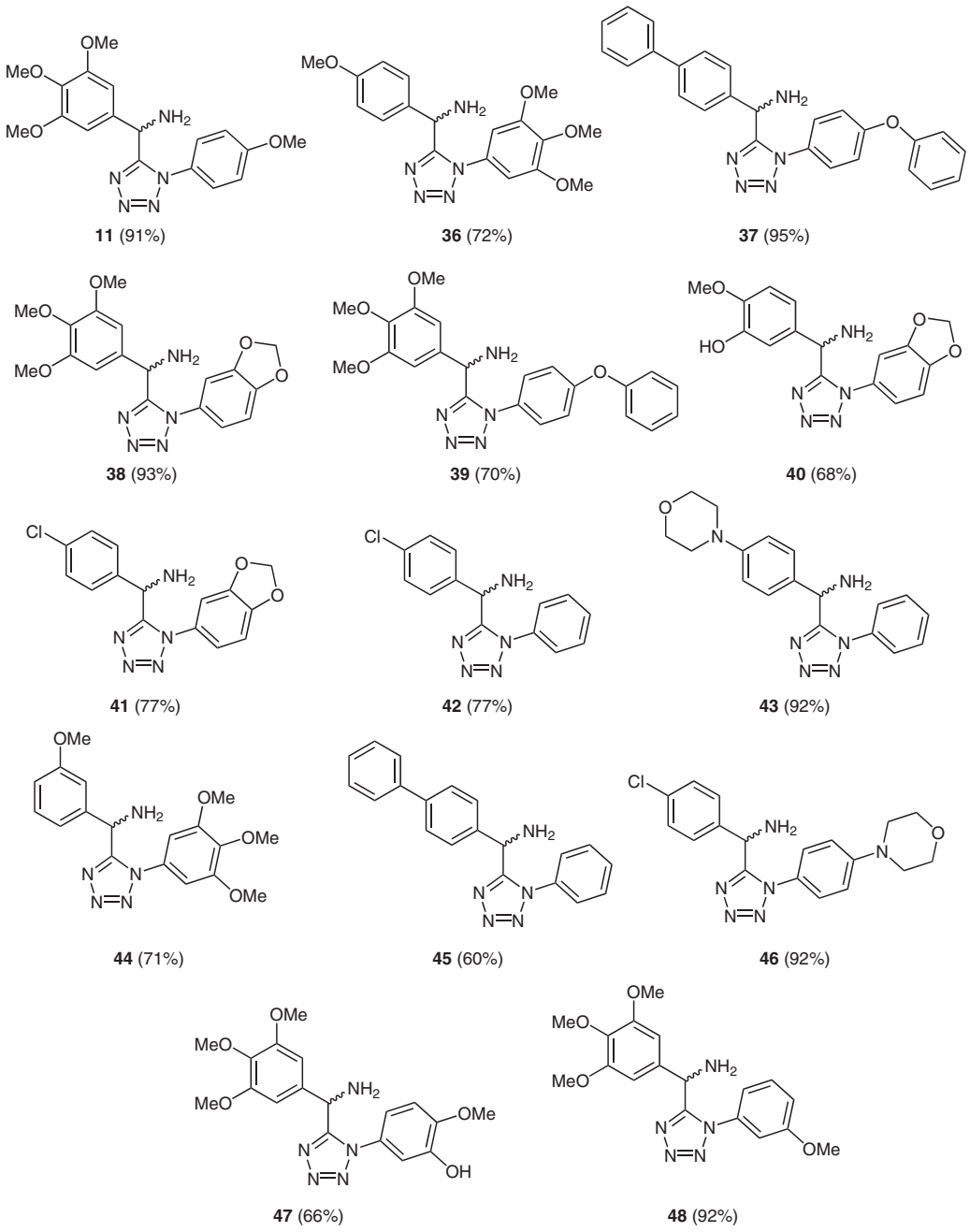


Figure 3 Hydrogenolysis products

MS (ESI): m/z = 462 $(M + H)^+$.

***N*-Benzyl-1-[1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl]-1-(3,4,5-trimethoxyphenyl)methanamine (23)**

The crude material was purified by column chromatography using PE–EtOAc (6:4) as eluent to give a yellowish oil (70%).

IR (KBr): 3288, 2326, 1275, 1128, 749, 764 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.12–7.04 (m, 5 H), 7.01 (d, J = 8.2 Hz, 2 H), 6.70 (d, J = 8.2 Hz, 2 H), 6.23 (s, 2 H), 4.93 (s, 1 H), 3.75 (s, 3 H), 3.764 (s, 3 H), 3.55 (s, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 155.8, 153.0, 138.8, 138.5, 128.6, 127.9, 127.7, 126.7, 113.7, 102.6, 60.4, 55.7, 54.9, 54.7, 50.5.

MS (ESI): m/z = 462 $(M + H)^+$.

***N*-Benzyl-1-(biphenyl-4-yl)-1-[1-(4-phenoxyphenyl)-1*H*-tetrazol-5-yl]methanamine (24)**

The crude material was purified by column chromatography using PE–EtOAc (8:2) as eluent to give a brown oil (74%).

IR (KBr): 3291, 2360, 2341, 1521, 1237, 733, 788, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.59–6.97 (m, 23 H), 5.12 (s, 1 H), 3.80 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 156.4, 155.8, 141.5, 140.3, 138.9, 137.0, 130.3, 129.0, 128.6, 128.5, 128.4, 127.7, 127.2, 124.8, 120.0, 118.7, 55.6, 51.2.

MS (ESI): m/z = 510 $(M + H)^+$.

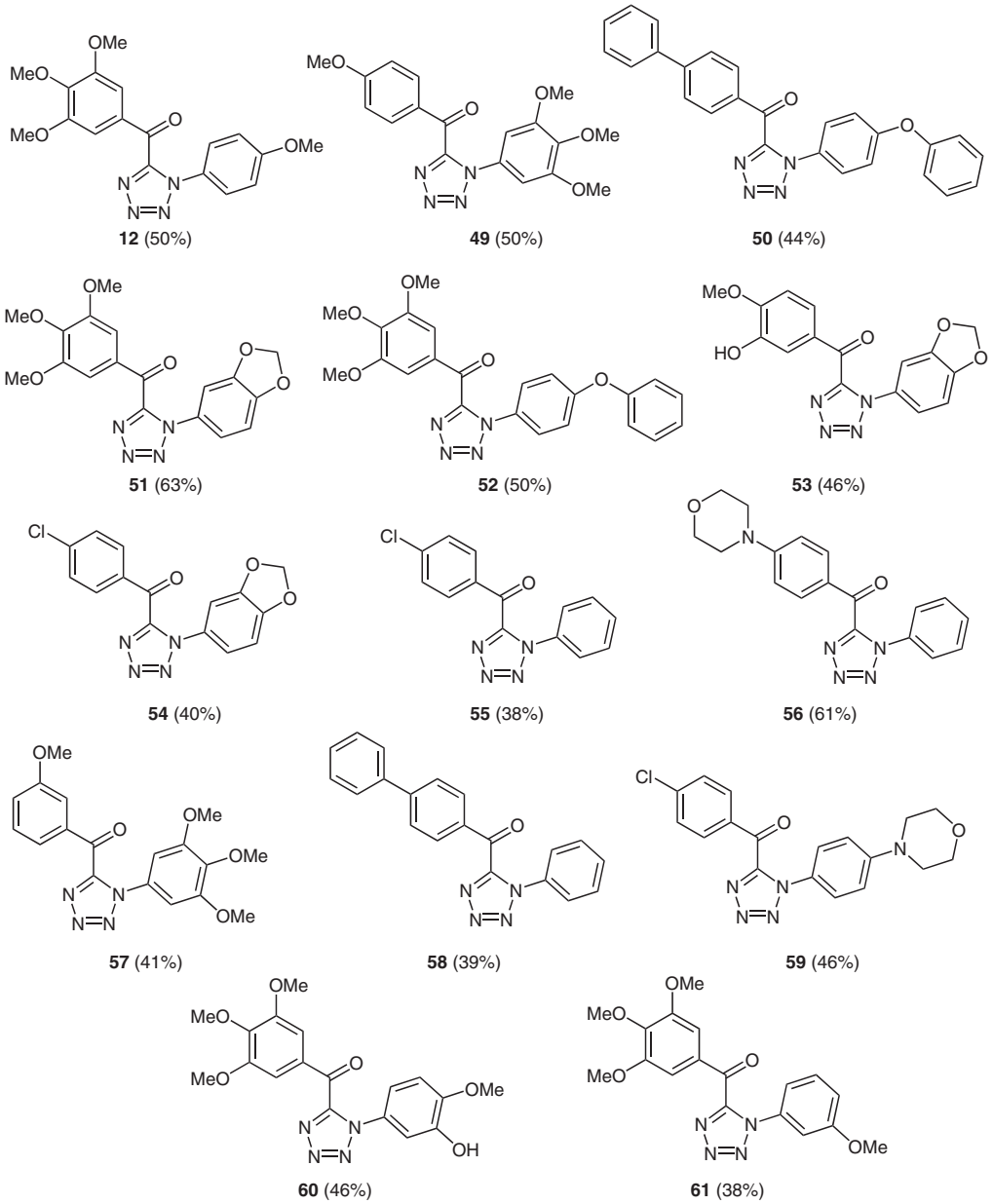


Figure 4 Synthesized 5-aroyl-1-aryltetrazoles

1-[1-(Benzo[*d*][1,3]dioxol-5-yl)-1*H*-tetrazol-5-yl]-*N*-benzyl-1-(3,4,5-trimethoxyphenyl)methanamine (25)

The crude material was filtered under vacuum and washed with cold MeOH to give a pale yellow solid (78%); mp 123–126 °C.

IR (KBr): 3278, 2925, 1502, 1323, 1131, 894, 747 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.23 (m, 5 H), 6.78 (d, *J* = 8.2 Hz, 1 H), 6.61–6.56 (m, 2 H), 6.41 (s, 2 H), 6.05 (s, 2 H), 4.89 (s, 1 H), 3.79 (s, 3 H), 3.75 (s, 6 H), 3.72 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 153.6, 149.5, 148.4, 138.7, 138.1, 133.4, 128.6, 128.5, 127.5, 127.0, 119.8, 108.4, 106.9, 104.9, 102.5, 60.9, 56.4, 56.3, 51.3.

MS (ESI): *m*/*z* = 476 $(M + H)^+$.

***N*-Benzyl-1-[1-(4-phenoxyphenyl)-1*H*-tetrazol-5-yl]-1-(3,4,5-trimethoxyphenyl)methanamine (26)**

The crude material was filtered under vacuum and washed with cold MeOH to give a pale yellow solid (86%); mp 126–130 °C.

IR (KBr): 3420, 1617, 1509, 1242, 1132, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–6.92 (m, 16 H), 6.38 (s, 2 H), 4.92 (s, 1 H), 3.76 (s, 2 H), 3.71 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 156.4, 155.6, 153.6, 138.9, 138.1, 133.4, 130.3, 128.6, 128.5, 127.9, 127.5, 127.4, 124.9, 120.0, 118.4, 104.9, 60.9, 56.3, 56.2, 51.2.

MS (ESI): *m*/*z* = 524 $(M + H)^+$.

5-{[(1-(Benzo[*d*][1,3]dioxol-5-yl)-1*H*-tetrazol-5-yl](benzylamino)methyl}-2-methoxyphenol (27)

The crude material was purified by column chromatography using PE–EtOAc (6:4) as eluent to give a colorless oil (53%).

IR (KBr): 3290, 2361, 1505, 1246, 1270, 1033, 743, 730, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.16 (m, 5 H), 6.79 (d, *J* = 2.1 Hz, 1 H), 6.72 (d, *J* = 8.3 Hz, 1 H), 6.64 (dd, *J* = 8.3, 2.1 Hz, 1 H), 6.54 (m, 1 H), 6.51 (d, *J* = 2.3 Hz, 1 H), 5.99 (s, 2 H), 4.86 (s, 1 H), 3.78 (s, 3 H), 3.67 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 149.6, 148.6, 147.2, 146.4, 138.9, 131.0, 128.6, 128.6, 127.5, 127.0, 119.7, 119.6, 114.5, 111.2, 108.5, 106.8, 102.6, 60.6, 56.2, 55.5, 51.2.

MS (ESI): *m*/*z* = 432 $(M + H)^+$.

1-[1-(Benzo[*d*][1,3]dioxol-5-yl)-1H-tetrazol-5-yl]-*N*-benzyl-1-(4-chlorophenyl)methanamine (28)

The crude material was purified by column chromatography using PE–EtOAc (8:2) as eluent to give a colorless oil (87%).

IR (KBr): 3283, 1505, 1244, 1035, 811, 732, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.12 (m, 9 H), 6.68 (m, 1 H), 6.54–6.48 (m, 3 H), 5.96 (s, 2 H), 4.93 (s, 1 H), 3.62 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 149.6, 148.7, 138.8, 136.7, 134.5, 129.5, 129.2, 128.9, 128.5, 127.5, 126.9, 119.7, 108.5, 106.7, 102.7, 60.5, 55.2, 51.2.

MS (ESI): *m*/*z* = 420 $(M + H)^+$.

***N*-Benzyl-1-(4-chlorophenyl)-1-(1-phenyl-1*H*-tetrazol-5-yl)methanamine (29)**

The crude material was purified by column chromatography using PE–EtOAc (9:1) as eluent to give a colorless oil (65%).

IR (KBr): 3295, 1492, 1091, 1015, 702, 762, 736, 691 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.34 (m, 3 H), 7.23–7.09 (m, 11 H), 4.99 (s, 1 H), 3.67 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 139.2, 137.1, 134.9, 133.9, 131.3, 130.3, 129.9, 129.6, 129.5, 129.1, 128.9, 128.4, 127.9, 125.9, 55.7, 51.6.

MS (ESI): *m*/*z* = 389 $(M + H)^+$.

***N*-Benzyl-1-(4-morpholinophenyl)-1-(1-phenyl-1*H*-tetrazol-5-yl)methanamine (30)**

The crude material was filtered under vacuum and washed with cold MeOH to give an off-white solid (71%); mp 89–93 °C.

IR (KBr): 3238, 2812, 1513, 1263, 1112, 921, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 3 H), 7.17–7.05 (m, 8 H), 6.73 (d, *J* = 8.1 Hz, 2 H), 4.89 (s, 1 H), 3.69 (br s, 4 H), 3.62 (s, 2 H), 3.01 (br s, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 151.9, 139.7, 134.2, 131.2, 130.4, 129.4, 129.1, 129.1, 127.9, 126.0, 116.2, 67.4, 55.9, 51.7, 49.5.

MS (ESI): *m*/*z* = 450 $(M + Na)^+$.

***N*-Benzyl-1-[2-(3-methoxyphenyl)-2*H*-tetrazol-5-yl]-1-(3,4,5-trimethoxyphenyl)methanamine (31)**

The crude material was purified by column chromatography using PE–EtOAc (6:4) as eluent to give a yellow oil (63%).

IR (KBr): 3288, 1592, 1460, 1235, 1124, 729, 688 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (m, 6 H), 6.63 (br t, 3 H), 6.22 (s, 2 H), 4.93 (s, 1 H), 3.68 (s, 3 H), 3.59 (s, 2 H), 3.54 (s, 3 H), 3.49 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3, 157.1, 154.5, 139.8, 138.9, 135.4, 134.4, 131.4, 129.5, 129.3, 128.3, 118.6, 117.6, 112.2, 105.8, 61.7, 57.4, 57.1, 56.6, 52.2.

MS (ESI): *m*/*z* = 462 $(M + H)^+$.

***N*-Benzyl-1-(biphenyl-4-yl)-1-(2-phenyl-2*H*-tetrazol-5-yl)methanamine (32)**

The crude material was purified by column chromatography using PE–EtOAc (8:2) as eluent to give a colorless oil (69%).

IR (KBr): 3286, 1597, 1453, 1101, 1008, 761, 733, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.16 (m, 18 H), 5.11 (s, 1 H), 3.76 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 142.1, 141.0, 139.6, 137.7, 134.2, 131.4, 130.5, 129.7, 129.3, 129.2, 129.1, 128.6, 128.4, 128.4, 128.1, 127.8, 126.1, 56.3, 51.9.

MS (ESI): *m*/*z* = 418 $(M + H)^+$.

***N*-Benzyl-1-(4-chlorophenyl)-1-[1-(4-morpholinophenyl)-1*H*-tetrazol-5-yl]methanamine (33)**

The crude material was purified by column chromatography using PE–EtOAc (6:4) as eluent to give a yellow oil (82%).

IR (KBr): 3290, 1521, 1450, 1236, 1120, 926, 823, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.12 (m, 9 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 4.94 (s, 1 H), 3.75 (m, 4 H), 3.62 (s, 2 H), 3.13 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8, 153.2, 139.5, 137.6, 134.9, 130.1, 129.7, 129.3, 129.1, 128.1, 127.1, 124.8, 115.8, 67.3, 55.9, 51.8, 48.9.

MS (ESI): *m*/*z* = 461 $(M + H)^+$.

5-{(Benzylamino)[1-(3,4,5-trimethoxyphenyl)-1*H*-tetrazol-5-yl]methyl}-2methoxyphenol (34)

The crude material was filtered under vacuum and washed with cold MeOH to give a yellow solid (75%); mp 130–134 °C.

IR (KBr): 3284, 2835, 1509, 1465, 1232, 1133, 999 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.12 (m, 5 H), 6.77 (s, 1 H), 6.68 (d, *J* = 8.3 Hz, 1 H), 6.59 (dd, *J* = 8.3, 2.2 Hz, 1 H), 6.29 (s, 2 H), 4.89 (s, 1 H), 3.85 (s, 3 H), 3.77 (s, 3 H), 3.66 (s, 6 H), 3.36 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8, 154.1, 147.7, 146.9, 139.9, 139.3, 131.4, 129.2, 129.1, 128.9, 127.9, 120.1, 115.1, 111.6, 103.7, 61.6, 56.9, 56.6, 56.2, 51.6, 51.0.

MS (ESI): *m*/*z* = 478 $(M + H)^+$.

***N*-Benzyl-1-(3-methoxyphenyl)-1-[1-(3,4,5-trimethoxyphenyl)-1*H*-tetrazol-5-yl]methanamine (35)**

The crude material was purified by column chromatography using PE–EtOAc (7:3) as eluent to give a colorless oil (81%).

IR (KBr): 3286, 1508, 1232, 1131, 1126, 735, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07–7.01 (m, 5 H), 6.66–6.60 (m, 3 H), 6.22 (s, 2 H), 4.93 (s, 1 H), 3.68 (s, 3 H), 3.59 (s, 2 H), 3.55 (s, 3 H), 3.49 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2, 157.1, 154.5, 139.8, 138.9, 135.4, 134.4, 131.3, 129.5, 129.3, 128.3, 118.6, 117.6, 112.2, 105.8, 78.7, 78.3, 77.8, 61.7, 61.3, 57.4, 57.1, 56.6, 52.2.

MS (ESI): *m*/*z* = 475 $(M + H)^+$.

[1-(4-Methoxyphenyl)-1*H*-tetrazol-5-yl](3,4,5-trimethoxyphenyl)methanamine (11)

Yellow-brown solid (91%); mp 123–125 °C.

IR (KBr): 3372, 3290, 2359, 1517, 1257, 1122, 834, 764 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.01 (d, *J* = 8.3 Hz, 2 H), 6.84 (d, *J* = 8.3 Hz, 2 H), 6.26 (s, 2 H), 5.14 (s, 1 H), 3.75 (s, 3 H), 3.68 (s, 3 H), 3.62 (s, 6 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 160.4, 156.9, 152.8, 137.1, 134.8, 126.4, 126.1, 125.2, 113.9, 103.2, 60.0, 55.8, 55.3, 50.6.

MS (ESI): *m*/*z* = 372 $(M + H)^+$.

(4-Methoxyphenyl)[1-(3,4,5-trimethoxyphenyl)-1*H*-tetrazol-5-yl]methanamine (36)
White solid (72%); mp 132–135 °C.

IR (KBr): 3335, 3276, 2999, 1601, 1242, 1128, 1002, 848 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.12 (d, *J* = 8.2 Hz, 2 H), 6.81 (d, *J* = 8.2 Hz, 2 H), 6.35 (s, 2 H), 5.24 (s, 1 H), 3.86 (s, 3 H), 3.76 (s, 3 H), 3.68 (s, 6 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 159.1, 153.1, 138.9, 128.3, 127.9, 113.9, 102.7, 60.5, 55.8, 54.9, 50.4.

MS (ESI): *m*/*z* = 394.2 $(M + Na)^+$.

Biphenyl-4-yl[1-(4-phenoxyphenyl)-1*H*-tetrazol-5-yl]methanamine (37)
White solid (95%); mp 234–236 °C.

IR (KBr): 3420, 3330, 2852, 1588, 1240, 1166, 1008, 758 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.64–7.56 (m, 3 H), 7.47–7.14 (m, 8 H), 6.99–6.94 (m, 3 H), 6.12 (s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 159.9, 155.8, 152.8, 143.4, 139.4, 130.4, 129.9, 129.1, 128.8, 127.9, 127.7, 127.2, 126.7, 124.4, 119.4, 118.5, 49.8, 48.5.

MS (ESI): *m*/*z* = 420 $(M + H)^+$.

[1-(Benzo[*d*][1,3]dioxol-5-yl)-1*H*-tetrazol-5-yl](3,4,5-trimethoxyphenyl)methanamine (38)
White solid (93%); mp 95–98 °C.

IR (KBr): 3323, 3280, 2901, 1425, 1463, 1252, 1119, 1002, 860 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 6.90 (d, *J* = 8.2 Hz, 1 H), 6.78 (dd, *J* = 8.2, 2.1 Hz, 1 H), 6.70 (s, 1 H), 6.46 (s, 2 H), 6.06 (s, 2 H), 5.41 (s, 1 H), 3.71 (s, 6 H), 3.68 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 157.6, 153.5, 149.7, 148.5, 138.1, 134.3, 126.9, 120.2, 108.2, 106.8, 104.9, 102.8, 59.9, 55.5, 51.0.

MS (ESI): *m*/*z* = 386 $(M + H)^+$.

[1-(4-Phenoxyphenyl)-1*H*-tetrazol-5-yl](3,4,5-trimethoxyphenyl)methanamine (39)
White solid (70%); mp 75–79 °C.

IR (KBr): 3370, 3280, 2838, 1512, 1462, 1244, 1125, 1009, 839 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.42–6.98 (m, 9 H), 6.47 (s, 2 H), 5.64 (s, 1 H), 3.69 (s, 6 H), 3.67 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 171.7, 159.7, 156.5, 155.8, 153.6, 138.3, 130.1, 127.9, 127.7, 124.6, 119.7, 118.4, 105.1, 60.3, 59.9, 55.5.

MS (ESI): *m*/*z* = 434 $(M + H)^+$.

5-{Amino[1-(benzo[*d*][1,3]dioxol-5-yl)-1*H*-tetrazol-5-yl]methyl}-2-methoxyphenol (40)
Dark yellow amorphous solid (68%).

IR (KBr): 3368, 3300, 2602, 1852, 1508, 1256, 1028, 931, 890 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 6.89–6.83 (m, 2 H), 6.73–6.59 (m, 4 H), 6.06 (s, 2 H), 5.56 (s, 1 H), 3.80 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 155.7, 150.0, 148.9, 148.8, 147.1, 128.0, 126.6, 119.9, 119.5, 114.6, 111.9, 108.3, 106.5, 102.9, 55.4, 50.2.

MS (ESI): *m*/*z* = 342 $(M + H)^+$.

1-[1-(Benzo[*d*][1,3]dioxol-5-yl)-1*H*-tetrazol-5-yl](4-chlorophenyl)methanamine (41)
Off-white solid (77%); mp 238–241 °C.

IR (KBr): 3350, 3255, 2851, 1491, 1225, 1107, 893, 697 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.41–7.38 (m, 2 H), 7.22–7.26 (m, 2 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 6.72–6.67 (m, 2 H), 6.05 (s, 2 H), 6.01 (s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 152.9, 150.2, 148.9, 131.8, 130.6, 129.5, 128.6, 126.2, 119.8, 108.3, 106.3, 102.9, 50.0.

MS (ESI): *m*/*z* = 330 $(M + H)^+$.

(4-Chlorophenyl)(1-phenyl-1*H*-tetrazol-5-yl)methanamine (42)
Off-white solid (77%); mp 229–232 °C.

IR (KBr): 3300, 3278, 2853, 1560, 1458, 1258, 1075, 759, 530 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.59–7.19 (m, 9 H), 5.98 (s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 153.9, 136.4, 133.5, 133.3, 131.5, 130.7, 130.4, 130.3, 129.9, 128.8, 125.8, 50.1.

MS (ESI): *m*/*z* = 286 $(M + H)^+$.

(4-Morpholinophenyl)(2-phenyl-2*H*-tetrazol-5-yl)methanamine (43)
Yellowish oil (92%).

IR (KBr): 3367, 3296, 2360, 1515, 1231, 1118, 925, 749 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.54–7.46 (m, 3 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 7.02 (d, *J* = 8.1 Hz, 2 H), 6.81 (d, *J* = 8.3 Hz, 2 H), 5.46 (s, 1 H), 3.73 (br s, 4 H), 3.05 (br s, 4 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 157.7, 152.4, 134.1, 131.4, 130.4, 129.0, 126.1, 125.9, 116.4, 67.2, 50.8, 49.3.

MS (ESI): *m*/*z* = 337 $(M + H)^+$.

(3-Methoxyphenyl)[1-(3,4,5-trimethoxyphenyl)-1*H*-tetrazol-5-yl]methanamine (44)
Dark yellow oil (71%).

IR (KBr): 3376, 3289, 1601, 1463, 1125, 996, 774, 696 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.21 (br t, 1 H), 6.86–6.74 (m, 3 H), 6.55 (s, 2 H), 5.64 (s, 1 H), 3.77 (s, 3 H), 3.70 (s, 9 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 160.8, 157.1, 154.3, 140.2, 139.4, 130.8, 129.3, 120.3, 115.0, 114.2, 113.2, 104.4, 60.7, 56.4, 55.3, 51.4.

MS (ESI): *m*/*z* = 372 $(M + H)^+$.

Biphenyl-4-yl(2-phenyl-2*H*-tetrazol-5-yl)methanamine (45)
The reaction mixture was filtered through a Celite pad, evaporated under vacuum, and purified by column chromatography using PE–EtOAc (3:7) and then EtOAc as eluents to give a yellow amorphous solid (60%).

IR (KBr): 3410, 3300, 1617, 1116, 760, 692 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.44–7.10 (m, 14 H), 5.36 (s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 158.9, 141.7, 140.8, 139.6, 134.2, 131.3, 130.4, 129.4, 128.1, 127.9, 127.7, 127.4, 126.3, 51.2.

MS (ESI): *m*/*z* = 328 $(M + H)^+$.

(4-Chlorophenyl)[2-(4-morpholinophenyl)-2*H*-tetrazol-5-yl]methanamine (46)
Off-white solid (92%); mp 231–234 °C.

IR (KBr): 3371, 3290, 2859, 2630, 1523, 1451, 1237, 1126, 926, 697 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.42–7.34 (m, 2 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 7.09–7.01 (m, 5 H), 5.98 (s, 1 H), 3.84 (br s, 4 H), 3.24 (br s, 4 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 153.6, 152.4, 132.5, 131.3, 130.3, 129.3, 127.2, 125.6, 117.1, 66.9, 50.8, 50.0.

MS (ESI): *m*/*z* = 371 $(M + H)^+$.

5-{5-[Amino(3,4,5-trimethoxyphenyl)methyl]-2*H*-tetrazol-2-yl}-2-methoxyphenol (47)

Yellow solid (66%); mp 138–140 °C.

IR (KBr): 3400, 3300, 2839, 1507, 1464, 1126, 1017, 904, 867 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.00 (d, *J* = 8.1 Hz, 1 H), 6.70 (dd, *J* = 8.1, 2.2 Hz, 1 H), 6.60 (s, 1 H), 6.49 (s, 2 H), 5.89 (s, 1 H), 3.90 (s, 3 H), 3.72 (s, 9 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 154.6, 153.9, 150.7, 148.1, 140.0, 128.1, 126.3, 117.9, 113.3, 112.3, 106.6, 60.8, 56.3, 51.2.

MS (ESI): *m*/*z* = 386.1 $(M - H)^-$.

[1-(3-Methoxyphenyl)-1*H*-tetrazol-5-yl](3,4,5-trimethoxyphenyl)methanamine (48)

Brownish solid (92%); mp 227–230 °C.

IR (KBr): 3370, 3296, 2623, 1599, 1129, 1035, 988, 843 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.43 (br t, 1 H), 7.12 (dd, *J* = 8.1, 2.2 Hz, 1 H), 6.91 (d, *J* = 8.1 Hz, 1 H), 6.77 (s, 1 H), 6.54 (s, 2 H), 6.03 (s, 1 H), 3.75 (s, 3 H), 3.71 (s, 6 H), 3.69 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 161.6, 154.8, 153.7, 140.2, 134.8, 131.6, 127.9, 118.6, 117.8, 112.2, 106.9, 60.8, 56.5, 56.1, 51.1.

MS (ESI): *m*/*z* = 372 $(M + H)^+$.

[1-(4-Methoxyphenyl)-1*H*-tetrazol-5-yl](3,4,5-trimethoxyphenyl)methanone (12)

The crude material was purified by column chromatography, using PE–EtOAc (7:3) as eluent to give a yellowish solid (50%); mp 156–159 °C.

IR (KBr): 2945, 1655, 1472, 1339, 1133, 833, 775 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 2 H), 7.40 (d, *J* = 8.6 Hz, 2 H), 7.01 (d, *J* = 8.6 Hz, 2 H), 3.97 (s, 3 H), 3.90 (s, 6 H), 3.86 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.4, 160.7, 152.8, 149.6, 144.5, 129.1, 126.5, 126.0, 114.2, 108.0, 60.7, 55.9, 55.2.

MS (ESI): *m*/*z* = 371 $(M + H)^+$.

Anal. Calcd for $C_{18}H_{18}N_4O_5$ (370.1): C, 58.37; H, 4.90; N, 15.13. Found: C, 58.30; H, 5.10; N, 15.30.

[1-(4-Methoxyphenyl)-1*H*-tetrazol-5-yl](3,4,5-trimethoxyphenyl)methanone (49)

The crude material was purified by column chromatography using PE–EtOAc (7:3) as eluent to give a yellowish solid (50%); mp 134–135 °C.

IR (KBr): 2930, 1600, 1512, 1280, 1173, 1026, 926, 843 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 2 H), 7.40 (d, *J* = 8.2 Hz, 2 H), 7.01 (d, *J* = 8.2 Hz, 2 H), 3.97 (s, 3 H), 3.90 (s, 6 H), 3.86 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.7, 165.3, 153.2, 149.9, 139.2, 133.0, 129.1, 127.5, 114.1, 102.3, 60.6, 56.0, 55.4.

MS (ESI): *m*/*z* = 392 $(M + Na)^+$.

Anal. Calcd for $C_{18}H_{18}N_4O_5$ (370.1): C, 58.37; H, 4.90; N, 15.13. Found: C, 58.60; H, 5.15; N, 15.00.

Biphenyl-4-yl[2-(4-phenoxyphenyl)-2*H*-tetrazol-5-yl]methanone (50)

The crude material was purified by column chromatography using PE–EtOAc (7:3) as eluent to give an amorphous orange solid (44%).

IR (KBr): 2860, 1630, 1452, 1121, 1049, 734, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.3 Hz, 2 H), 7.76 (d, *J* = 8.3 Hz, 2 H), 7.65 (d, *J* = 8.2 Hz, 2 H), 7.51–7.37 (m, 5 H), 7.19 (br t, 1 H), 7.08 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.0, 159.8, 155.7, 150.1, 148.3, 139.4, 133.6, 131.7, 130.3, 129.2, 128.9, 128.6, 127.7, 127.5, 126.78, 124.8, 120.2, 118.5.

MS (ESI): *m*/*z* = 419 $(M + H)^+$.

Anal. Calcd for $C_{26}H_{18}N_4O_2$ (418.1): C, 74.63; H, 4.34; N, 13.39. Found: C, 74.80; H, 4.50; N, 13.40.

[2-(Benzo[*d*][1,3]dioxol-5-yl)-2*H*-tetrazol-5-yl](3,4,5-trimethoxyphenyl)methanone (51)

The crude material was purified by column chromatography using PE–EtOAc (7:3) as eluent to give a yellowish solid (63%); mp 109–112 °C.

IR (KBr): 2894, 1620, 1504, 1474, 1336, 1124, 995, 860 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 2 H), 6.93–6.88 (m, 3 H), 6.07 (s, 2 H), 3.95 (s, 3 H), 3.89 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.8, 153.3, 150.1, 149.6, 148.4, 145.0, 129.6, 127.8, 119.3, 108.5, 108.4, 106.4, 102.6, 61.2, 56.4.

MS (ESI): *m*/*z* = 385 $(M + H)^+$.

Anal. Calcd for $C_{18}H_{16}N_4O_6$ (384.1): C, 56.25; H, 4.20; N, 14.58. Found: C, 55.90; H, 4.00; N, 14.70.

[2-(4-Phenoxyphenyl)-2*H*-tetrazol-5-yl](3,4,5-trimethoxyphenyl)methanone (52)

The crude material was purified by column chromatography using PE–EtOAc (8:2) as eluent to give a yellowish solid (50%); mp 183–185 °C.

IR (KBr): 2831, 1630, 1507, 1414, 1383, 1244, 1127, 837 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (s, 2 H), 7.44–7.39 (m, 4 H), 7.18 (br t, 1 H), 7.10–7.05 (m, 4 H), 3.97 (s, 3 H), 3.90 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.0, 159.9, 155.7, 153.4, 150.2, 145.2, 130.4, 129.7, 128.7, 126.8, 124.9, 120.3, 118.5, 108.7, 61.3, 56.6.

MS (ESI): *m*/*z* = 433.06 $(M + H)^+$.

Anal. Calcd for $C_{23}H_{20}N_4O_5$ (432.1): C, 63.88; H, 4.66; N, 12.96. Found: C, 64.05; H, 4.80; N, 12.90.

[2-(Benzo[*d*][1,3]dioxol-5-yl)-2*H*-tetrazol-5-yl](3-hydroxy-4-methoxyphenyl)methanone (53)

The crude material was purified by column chromatography using EtOAc as eluent to give a light yellow solid (46%); mp 220–223 °C.

IR (KBr): 1645, 1505, 1282, 1126, 1036, 778 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.68 (d, *J* = 8.2 Hz, 1 H), 7.54 (s, 1 H), 7.27 (s, 1 H), 7.12–7.06 (m, 3 H), 6.16 (s, 2 H), 3.88 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 180.5, 155.2, 150.9, 149.7, 148.5, 147.5, 128.3, 128.1, 126.1, 120.3, 116.4, 112,3, 109.0, 107.4, 103.2, 56.7.

MS (ESI): *m*/*z* = 339.0 $(M - H)^-$.

Anal. Calcd for $C_{16}H_{12}N_4O_5$ (340.1): C, 56.47; H, 3.55; N, 16.46. Found: C, 56.60; H, 3.70; N, 16.70.

[2-(Benzo[*d*][1,3]dioxol-5-yl)-2*H*-tetrazol-5-yl](4-chloro-3-methylphenyl)methanone (54)

The crude material was purified by column chromatography using PE–EtOAc (7:3) as eluent to give a yellow solid (40%); mp 117–121 °C.

IR (KBr): 2920, 1635, 1471, 1383, 1035, 922, 616 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.22 (m, 2 H), 7.71 (br t, 1 H), 7.58–7.52 (m, 2 H), 6.95–6.89 (m, 2 H), 6.09 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.7, 149.8, 148.6, 135.7, 135.0, 132.5, 131.1, 129.3, 127.3, 119.6, 108.6, 102.7.

MS (ESI): *m*/*z* = 329 $(M + H)^+$.

Anal. Calcd for $C_{15}H_9ClN_4O_3$ (328.0): C, 54.81; H, 2.76; N, 17.04. Found: C, 55.00; H, 2.90; N, 16.90.

(4-Chlorophenyl)(2-phenyl-2*H*-tetrazol-5-yl)methanone (55)

4-Formyl-1-methylpyridinium benzenesulfonate (2.2 equiv) was used. The crude material was purified by column chromatography using PE–EtOAc (9:1) as eluent to give a white solid (38%); mp 85–87 °C.

IR (KBr): 1675, 1503, 1303, 918, 767 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.25–8.22 (m, 2 H), 7.70 (br t, 1 H), 7.57–7.46 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.2, 150.6, 136.2, 135.4, 134.8, 133.7, 133.0, 131.6, 131.4, 130.3, 130.1, 129.7, 125.8, 125.6.

MS (ESI): *m*/*z* = 285 $(M + H)^+$.

Anal. Calcd for $C_{14}H_9ClN_4O$ (284.0): C, 59.06; H, 3.19; N, 19.68. Found: C, 59.30; H, 3.40; N, 19.30.

(4-Morpholinophenyl)(2-phenyl-2*H*-tetrazol-5-yl)methanone (56)

The crude material was purified by column chromatography using PE–EtOAc (7:3) as eluent to give a yellow solid (61%); mp 164–167 °C.

IR (KBr): 1610, 1395, 1250, 1191, 929 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.2 Hz, 2 H), 7.51–7.46 (m, 5 H), 6.86 (d, *J* = 8.2 Hz, 2 H), 3.82 (br t, 4 H), 3.39 (br t, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.6, 156.3, 151.3, 135.1, 134.2, 131.2, 130.3, 125.7, 125.5, 113.6, 67.2, 47.6.

MS (ESI): *m*/*z* = 336.2 $(M + H)^+$.

Anal. Calcd for $C_{18}H_{17}N_5O_2$ (335.1): C, 64.47; H, 5.11; N, 20.88. Found: C, 64.45; H, 5.30; N, 20.80.

(3-Methoxyphenyl)[2-(3,4,5-trimethoxyphenyl)-2*H*-tetrazol-5-yl]methanone (57)

4-Formyl-1-methylpyridinium benzenesulfonate (2.2 equiv) was used. The crude material was purified by column chromatography using PE–EtOAc (7:3) as eluent to give a yellow solid (41%); mp 94–99 °C.

IR (KBr): 1632, 1506, 1339, 1277, 1127, 942 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.76 (m, 1 H), 7.66 (br t, *J* = 8.2 Hz, 1 H), 7.42 (br t, *J* = 8.1 Hz, 1 H), 7.25–7.05 (m, 1 H), 6.71 (s, 2 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.81 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.7, 161.1, 154.6, 151.1, 137.0, 131.2, 130.4, 125.0, 123.6, 123.5, 115.0, 103.8, 62.0, 57.5, 56.6.

MS (ESI): *m*/*z* = 371 $(M + H)^+$.

Anal. Calcd for $C_{18}H_{18}N_4O_5$ (370.1): C, 58.37; H, 4.90; N, 15.13. Found: C, 58.45; H, 5.10; N, 15.13.

Biphenyl-4-yl(2-phenyl-2*H*-tetrazol-5-yl)methanone (58)

The crude material was purified by column chromatography using PE–EtOAc (9:1) as eluent to give a white solid (39%); mp 129–132 °C.

IR (KBr): 1668, 1600, 1481, 1306, 924 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.2 Hz, 2 H), 8.76 (d, *J* = 8.2 Hz, 2 H), 7.65 (d, *J* = 8.2 Hz, 2 H), 7.56–7.43 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.7, 150.8, 148.9, 140.0, 134.2, 132.3, 131.7, 131.5, 130.4, 129.9, 129.6, 128.4, 128.2, 125.7.

MS (ESI): *m*/*z* = 327 $(M + H)^+$.

Anal. Calcd for $C_{20}H_{14}N_4O$ (326.1): C, 73.61; H, 4.32; N, 17.17. Found: C, 73.80; H, 4.56; N, 17.43.

(4-Chlorophenyl)[2-(4-morpholinophenyl)-2*H*-tetrazol-5-yl]methanone (59)

The crude material was purified by column chromatography using PE–EtOAc (6:4) as eluent to give a yellow solid (46%); mp 124–128 °C.

IR (KBr): 1640, 1520, 1447, 1303, 1113, 927, 819 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.93 (d, *J* = 8.4 Hz, 2 H), 3.84 (br t, 4 H), 3.23 (br t, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.6, 153.3, 150.7, 136.2, 135.7, 131.7, 129.8, 126.89, 126.8, 126.0 115.8, 67.5, 49.0.

MS (ESI): *m*/*z* = 370 $(M + H)^+$.

Anal. Calcd for $C_{18}H_{16}ClN_5O_2$ (369.1): C, 58.46; H, 4.36; N, 18.94. Found: C, 57.92; H, 4.24; N, 19.10.

[2-(3-Hydroxy-4-methoxyphenyl)-2*H*-tetrazol-5-yl](3,4,5-trimethoxyphenyl)methanone (60)

The crude material was purified by column chromatography using PE–EtOAc (7:3) as eluent to give a yellow solid (46%); mp 166–169 °C.

IR (KBr): 1643, 1514, 1255, 1124, 1021, 865 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 2 H), 7.01 (d, *J* = 2.1 Hz, 1 H), 7.97 (d, *J* = 2.1 Hz, 1 H), 6.94 (s, 1 H), 3.97 (s, 3 H), 3.94 (s, 3 H), 3.89 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.0, 154.2, 151.0, 149.4, 147.4, 145.9, 130.6, 128.3, 117.8, 112.7, 111.6, 109.4, 62.1, 57.4, 57.2.

MS (ESI): *m*/*z* = 385 $(M - H)^-$.

Anal. Calcd for $C_{18}H_{18}N_4O_6$ (386.1): C, 55.96; H, 4.70; N, 14.50: Found: C, 56.22; H, 4.83; N, 14.30.

[1-(3-Methoxyphenyl)-1*H*-tetrazol-5-yl](3,4,5-trimethoxyphenyl)methanone (61)

4-Formyl-1-methylpyridinium benzenesulfonate (2.2 equiv) was used. The crude material was purified by column chromatography using PE–EtOAc (6:4) as eluent to give a yellowish amorphous solid (38%).

IR (KBr): 1610, 1578, 1237, 1134, 842, 684 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 2 H), 7.40 (br t, 1 H), 7.08–6.97 (m, 3 H), 3.97 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.9, 161.3, 154.3, 154.2, 151.1, 131.4, 130.5, 118.0, 117.9, 117.5, 109.4, 62.2, 57.5, 57.4, 56.7.

MS (ESI): *m*/*z* = 371 $(M + H)^+$.

Anal. Calcd for $C_{18}H_{18}N_4O_5$ (370.1): C, 58.37; H, 4.90; N, 15.13. Found: C, 58.62; H, 4.95; N, 15.30.

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