Design and Synthesis of hydrazone derivatives of indole-tyrosine conjugates

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Abstract:

The synthesis of indole-tyrosine conjugate derivatives of hydrazoneis reported. Hydrazones arecharacterized by physical and spectroscopical methods. The different amino acids actas a linker such as tyrosine& systematic variation of the substituents on the aromatic ring revealed promising leads. Previous study showscompounds containing Tyr(Tyrosine) as the linker exhibited high anti-inflammatory activity.

Keywords:

Hydrazone,Amino acids, conjugation, Heterocyclic compound,Indole-tyrosine.

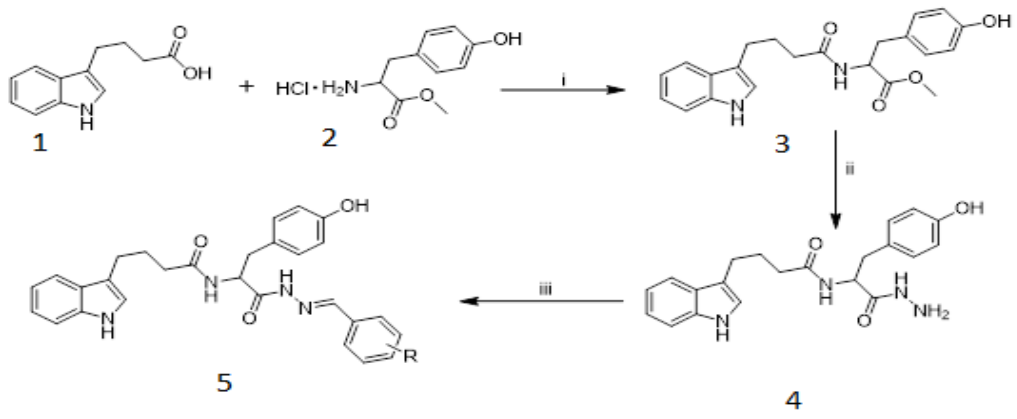
Introduction:

The main polypeptide chain of proteins has a distinctive sequence that typically consists of 20 canonical amino acids. The creation of Schiff bases & their complexes has involved the usage of amino acids. Such molecules have demonstrated promising outcomes when applied to a variety of biological functions, such as anti-inflammatory actions. Bioconjugation reactions either stay ahead of the biomolecule's inherent chemical reactivity or add extrinsic and intrinsic capabilities.Amino acids,changethe drug conformation, to helpthe preoccupation of the drugs. Further, amino acids are used to decrease the toxicity of drugs.

Tyrosine (Tyr) or 4-hydroxyphenylalanine is one of the 20aminoacidis usedto make a protein. tyrosine moleculescan combinewith a phosphate group (phosphorylated) by protein kinases, it containing polar groups,4-hydroxyphenylalanineis called phosphotyrosine. It is used for the signal transduction and regulation of enzymatic activity. antibodies are used to detect Phosphotyrosine.The sulfate group is combined with Tyrosine sulfotyrosine. In the brain,the tyrosine hydroxylase enzyme converts thetyrosine into L-dopa which is useful for the synthesisofthe neurotransmitter dopamine. Dopamine ischanged tocatecholamines, norepinephrine & epinephrine. (adrenaline). (A Dinu, C Apetrei - International Journal of Molecular Sciences, 2022 - mdpi.com &J Bargon, H Heinrich, U Bommerich, RR Rizi - afni.nimh.nih.gov)

For drug development Hydrazones is a very important molecule. These compounds showantimicrobial, anti-inflammatory, antidepressant, anticonvulsant, antimalarial, analgesic, antitubercular, antiviral, anticancer, etc. activities. The compounds contain a C=N bond, which is conjugated with a functional nitrogen atom. Thehydrazones containnitrogen &carbon atoms. The biological and pharmacological properties of these compounds are very important. The literature is enhancedwith numerous examples of hydrazone derivatives(guanylhydrazones,imidazole hydrazone derivatives[IA])and their biological activities, but we have highlighted here some of the activity profiles of these compounds.(J de Oliveira Carneiro Brum… -Minireviewin..2020-ingentaconnect.com&MichaelTapera[a]HüseyinKekeçmuhammed[a]BurakTüzünb,EminSarıpınaraÜmit,M.Koçyiğit[c]EbrarYıldırım[c]MuratDoğan[d]YunusZorlu[e])

Design andSynthesis



Reagent and conditions:i) EDCI/HOBt, DCM, Et_3N, 0 °Cat room temperature; ii) $NH_2NH_2.H_2O$, ethanol, reflux, 16h; iii) R-C_4H_4-CHO, ethanol, reflux, 8h

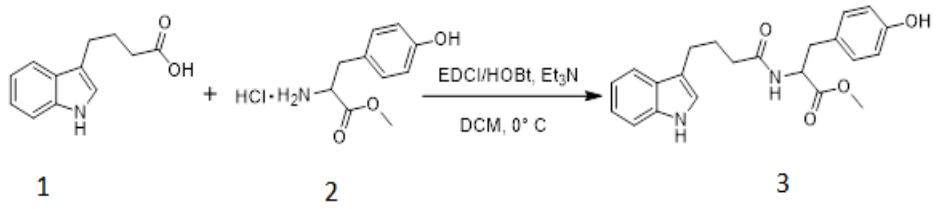
Scheme 1: Schematic representation of the synthesis of hydrazonederivatives of indole-tyrosine conjugates.

Experimental section:

A heterocyclic compound like indole-3-butyric acidwas purchasedfrom Avra Synthesis, Bengaluru.thedifferent substituted aldehydes, Et_3N, EDCI, HOBt, and hydrazine hydrate were bought from Sigma Aldrich, Bengaluru. The chemicalsare used in the synthesis of analytical compounds. The reaction was observed by using TLC plates with the solvent system containing chloroform/ acetic acid/methanol in the ratio 98:03:02 (R_f^a), 95:03:05 (R_f^b), 90:03:10 (RFC) and 95:03:15(R_f^d). The TLC plates were noticed by UV light. MPwas found by using the Superfit melting point apparatus (India). DMSO-d_6 was used as a

solventin^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra, (USA) using. Bruker MicroTOF QII mass spectrometer is used.

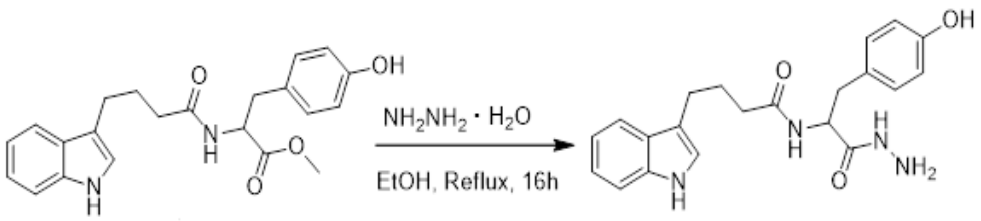
1.1 Synthesis of methyl-2-(4-(1H-indol-3-yl)-butanamido-3-(4-hydroxyphenyl)propanoate



1 2 3

Indole-3-butyric acid (2.0 g, 0.0098 mol)was stirred withDCM (10 mL/g of a compound) solution, this stirred solutionwas coolto 0 °C &furtherEt$_3$N (2.05 mL, 0.0147 mol)& EDCI (2.26 g, 0.0118 mmol) was added &keeping 0 °C temperature. the solution was shakenup toten minutes then add HOBt (1.50 g, 0.0098 mol) for another 10 minutes should be stirred. Then gradually addition ofEt$_3$N (2.05 mL, 0.0147 mol) in DCM (10 mL/g of a substance) &tyrosine methyl ester hydrochloride(2.27 g, 0.0098 mmol). Maintain the stirring condition overnight at room temperature&maintained at a pH was up to 8 by the addition of Et$_3$N,the reaction wasdone, and itis observed by TLC. The product was cleanedsuccessively with 5% sodium bicarbonate solution (2x50 mL), H$_2$O (2x50 mL), 0.1N HCl cold solution (2x50 mL), and finally salt water (2x50 mL) solution. Theproducts were trituratedfrom ether/pet.ether to get the wanted productsmethyl 2,4(1H-indol-3-yl)butanamido-3-(4-hydroxyphenyl)propanoate **(3)**.

1.2 Synthesis of N-(1-hydrazinyl-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-4-(1H-indol-3-yl)butanami

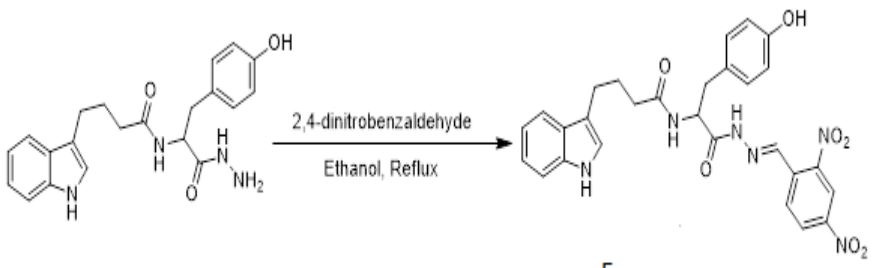


3 4

The hydrazine hydrate (3.80 mL, 0.0799 mol) is mixedwith amethyl 2,4(1H-indol-3-yl)butanamido-3(4-hydroxyphenyl)propanoate (**3**) (3.4 g, 0.0079mol) in ethanol (30 mL). the

reaction mixtureis refluxed up to16 h, the reaction is completed, & it is observed by TLC. Under reduced pressure solvent waswashed off and cooled by the additionof ice-cold water to get a precipitate, then it is filtered, cleaned with cold water, and recrystallizedthen obtained product isN-(1-hydrazinyl-3(4-hydroxyphenyl)1-oxopropan-2-yl-4(1H-indol-3-yl)butanami (**4**).

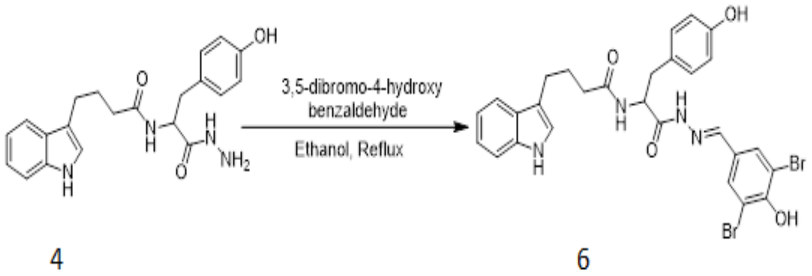
1.3 Synthesis of (E)-N-(1-(2-(2,4-dinitrobenzylidene)-hydrazinyl)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-4-(1H-indol-3-yl)-butanamide



4 5

Indole-tyrosine hydrazide (200 mg, 0.525 mmol)solutionis taken in ethanol(10 mL/g of the substance),&add 2,4-dinitrobenzaldehyde (103 mg, 0.525 mmol) solution. it isrefluxed upto7–8 h,reaction should be completed, it is measured by TLC. Under reduced pressure solvent was washed off &cooled by the addition of ice-cold water to get aprecipitate then it is filtered, cleaned with water, and recrystallizedfrom ethanol,it gives the wantedproduct (E)-N(1-2-(2,4-dinitrobenzylidene)-hydrazinyl)-3(4-hydroxyphenyl)-1-(oxopropan-2-yl)-4(1H-indol-3-yl)butanamide (**5)**.

1.4 Synthesis of (E)-N-(1-(2-(3,5-dibromo-4-hydroxybenzylidene)hydrazinyl)-3(4-hydroxyphenyl)1-oxopropan-2-yl)4(1H-indol-3-yl)butanamide



4 6

Indole-tyrosine hydrazide (200 mg, 0.525 mmol) was taken in ethanol(10 mL/g of the compound),&add 3,5-dibromo-4-hydroxybenzaldehyde (146 mg, 0.525 mmol). it is refluxed for 7–8 h and the reaction should be completed, it is measured by TLC.Under reduced pressure solvent was washed off and cooled by the addition of ice-cold water to get aprecipitate then it is filtered, washed with water, and recrystallizedfrom ethanol,it gives the wanted product(E)-N(1-(2-(3,5-dibromo-4-hydroxybenzylidene)hydrazinyl)-3(4-hydroxyphenyl)1-oxopropan-2-yl)4(1H-indol-3-yl)butanamide (**6)**.

NO.	Side chain of amino acids(R)	Yield %	Molecular formula	Elemental analysis, %				1H NMR (DMSO-d6, δ ppm)	^{13}C-NMR (DMSO-d_6)
				C	H	N	O		
3	Methyl-2-(4-(1H-indol-3-yl)-butanamido-3-(4-hydroxyphenyl) propanoate	85.2	$C_{22}H_{24}N_2O_4$	69.46	6.36	7.36	16.82	10.73 (s, 1H, Indole-NH), 9.21 (s, 1H, OH), 8.24-8.22 (d, 1H, Amide-NH), 7.45-6.91 (m, 9H, Ar-H), 4.37-4.35 (m, 1H, CH), 3.55 (s, 3H, OCH_3), 2.89-2.71 (d, 2H, Tyr-CH_2), 2.59-2.55 (t, 2H, CH_2), 2.12-2.09 (t, 2H, CH_2), 1.80-1.75 (m, 2H, CH_2)	172.88,172.16, 156.38, 136.71, 130.39, 127.76, 127.57, 122.66, 121.22, 118.74, 118.52, 115.43, 114.50, 111.73, 54.32, 52.15, 36.37, 35.19
4	N-(1-hydrazinyl-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-4-(1H-indol-3-yl)-butanami	80.5	$C_{25}H_{32}N_4O_3$	66.30	6.36	14.73	12.62	10.71 (s, 1H, Indole-NH), 9.14 (s, 1H, OH), 9.13 (s, 1H, Hydrazide-NH), 8.00-7.97 (d, 1H, Amide-NH), 7.45-6.60 (m, 9H, Ar-H), 4.41-4.35 (m, 1H, CH), 4.19 (s, 2H, Hydrazide-NH_2), 2.81-2.54 (m, 2H, Tyr-CH_2), 2.52-2.46 (t, 2H, CH_2), 2.11-2.08 (t, 2H, CH_2), 1.77-1.72 (m, 2H, CH_2)	172.35, 171.24 156.15, 136.72, 130.47, 128.49, 127.60, 122.63, 121.22, 118.78, 118.52, 115.28, 114.63, 111.72, 53.36, 37.64, 35.49, 26.43, 24.69
5	(E)-N-(1-(2-(2,4-dinitrobenzylidene)-hydrazinyl)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-4-(1H-indol-3-yl)-butanamide	75.08	$C_{28}H_{26}N_6O_7$	60.21	4.69	15.05	20.05	10.82 (s, 1H, Indole-NH), 9.22 (s, 1H, Hydrazide-NH), 9.21 (s, 1H, OH), 8.70 (s, 1H, -N=CH-), 8.09-8.04 (d, 1H, Amide-NH), 8.02-7.10 (m, 12H, Ar-H), 4.49-4.43 (m, 1H, CH), 2.98-2.73 (d, 2H, Phe-CH_2), 2.57-2.42 (t, 2H, CH_2), 2.08-2.03 (t, 2H, CH_2), 1.79-1.61 (m, 2H, CH_2)	175.42, 173.28, 155.69, 151.36, 148.02, 143.67, 136.80, 136.52, 134.58, 131.22, 130.62, 128.62, 127.83, 127.57, 125.93, 123.20, 121.55, 119.55, 118.41, 111.92, 110.50, 59.41, 37.63, 36.29, 28.92, 28.50
6	(E)-N-(1-(2-(3,5-dibromo-4-hydroxybenzylidene) hydrazinyl)-3(4-hydroxyphenyl)1-oxopropan-2-yl)4(1H-indol-3-yl) butanamide	93.17	$C_{28}H_{26}Br_2N_4O_4$	52.36	4.08	8.72	9.96	10.70 (s, 1H, Indole-NH), 9.34 (s, 1H, Hydrazide-NH), 9.23 (s, 2H, OH), 8.72 (s, 1H, -N=CH-), 8.08-8.05 (d, 1H, Amide-NH), 7.60-7.11 (m, 11H, Ar-H), 4.48-4.42 (m, 1H, CH), 2.97-2.72 (d, 2H, Phe-CH_2), 2.6-2.41 (t, 2H, CH_2), 2.09-2.04 (t, 2H, CH_2), 1.78-1.62 (m, 2H, CH_2)	175.88, 173.43, 155.80, 155.62, 143.88, 136.86, 136.58, 135.46, 132.59, 128.63, 127.82, 127.50, 126.37, 125.92, 123.10, 121.52, 119.52, 118.40, 111.93, 110.56, 59.45, 37.72, 3637, 28.90, 28.55

Table 1: Spectral data of the synthesized 3,4,5 &6 compounds.

Discussion

We report the Synthesis of hydrazone derivatives of indole-tyrosine conjugates.It starts from the Conjugation of indole-3-butyric acid with tyrosine methyl ester hydrochloride in presence of EDCI/ HOBtas a coupling agent and Et_3N as a base, to get indole-tyrosine ester conjugates. The change of indole-tyrosine ester into hydrazide by using hydrazine hydrate. Then indole-tyrosine hydrazide is treated with different substituted aldehydes &acts as a Schiff base to get the final desired hydrazone derivatives of the indole-tyrosine conjugates.Thecompletion of the reaction was measured by TLC plates . The compound yield is~93%,synthesized compounds are characterized by R_f values,M.P, ^{1}H NMR,^{13}C NMR, IR, mass spectral data & elemental analysis.The Rf values range from 0.3 -0.6, melting point is 109-111^{o}C. In NMR spectra,the singlet occurs at 10.70 for the indole-NH group, and also the singlet occurs at 9.34 for the Hydrazide-NH group.^{13}C NMR values occur at δ~175.88. The FTIR, ATR (cm^{-1}) data of compound(3) is3415-3250 for the NH group, 3200-3050 for the OH group, 1745-1690 for the CO group, the compound (4) having FTIR, ATR (cm^{-1})data is 3415-3250 for the NH group, 3200-3050 for the OH group, 1715-1695 for the CO group, the compound (5) having FTIR, ATR (cm^{-1})data is 3415-3250 for the NH group, 3200-3050 for the OH group, 1715-1695 for the CO group, 1690-1640 for the C=N group, the compound (6) having FTIR, ATR (cm^{-1})data is: 3415-3250 for the NH group, 3200-3050 for the OH group, 1715-1695 for the CO group, 1690-1640 for the C=N group.From elemental analysis % of the element can be confirmed, and all these data are represented in Table 1.

Result

The recent work explains, the conjugation of a heterocycle with an amino acid to form an amide bond,increases biological activities(65,66&67).The presence of electron-withdrawing groups increases the activitybecause it depends upon the moiety(68),and also the halogens present on the aromatic ring increase the activity because the activity depends on the electronegativity(69).The coupling reaction is very important for amide bond formation.Also, tyrosine is a side-chain amino acid it increases the activity.

Conclusion

The bi-functional compounds are formed from the conjugation methodologyused in drugchemistry. The binding capacity of the peptide is determined by the Coupling of

aquaphobic peptideswith bio-active molecules,upgradedpharmacologicproperties, &enlarged metabolic stability, oral availability, and cell permeability.However,in this paper, Indole is Conjugated with amino acids; it increases the beneficial property of the molecule. It controls bacterial activity. It is a naturally occurring alkaloid, Indole-tyrosine is a biologically very active compound, it shows anti-inflammatory activity. It indicates one of the important methods of synthesis of hydrazone derivatives of indole-tyrosine conjugates and it is helpful to cure diseases in the medical field. The conjugation of peptides with bioactive scaffolds plays a pivotal role in biomedical research.

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